

CLAIMS

We claim:

1. An ICE inhibitor comprising:
- (a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;
- (b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and
- (c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.
2. The ICE inhibitor according to claim 1, wherein said inhibitor is characterized by a neutral or favorable enthalpic contribution from the sum of all electrostatic interactions between the inhibitor and ICE when the inhibitor is bound thereto.
3. The ICE inhibitor according to claim 1, wherein said inhibitor has a molecular weight less than or equal to about 700 Daltons.

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4. The ICE inhibitor according to claim 3, wherein said inhibitor has a molecular weight between about 400 and about 600 Daltons.

5. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises less than two secondary amide bonds.

6. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises less than two groups selected from the set consisting of secondary amide groups and carbamate groups.

7. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises a polysubstituted cyclic group having between three and seven substituents, said cyclic group not comprising the first or second moderately hydrophobic moiety or the electronegative moiety.

8. The ICE inhibitor according to claim 1 or 7, wherein said inhibitor is characterized by a strain energy of binding of said inhibitor to ICE less than or equal to about 10 kcal/mole.

9. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE at least two of the following four conditions 1) through 4) are met:

1) one of said moderately hydrophobic moieties associates with the P2 binding pocket of ICE, in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P2

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binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 7.1Å and about 12.5Å;

5 b) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

10 c) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å;

2) one of said moderately hydrophobic moieties associates with the P3 binding pocket of ICE in such a way that:

15 a) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

20 b) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

25 c) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 7.0Å and about 13Å;

3) one of said moderately hydrophobic moieties associates with the P4 binding pocket of ICE in such a way that:

30 a) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 4.5Å and about 7.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P4

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binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.5Å and about 8.5Å; and

5 c) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 11Å; and

4) one of said moderately hydrophobic moieties associates with the P' binding pocket of ICE in such a way that:

10 a) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 11Å and about 16Å;

15 b) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the amide nitrogen of Arg-341 of ICE is between about 10Å and about 15Å; and

20 c) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 12Å.

10. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE, said moderately hydrophobic moieties separately
25 associate with the P' binding pocket of ICE and the P2 binding pocket of ICE and the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the center of mass of the moderately hydrophobic moiety in the P2 binding
30 pocket is between about 6.5Å and about 13Å.

11. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE,

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5 said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P' binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
pocket is between about 6Å and about 15Å.

10 12. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P' binding pocket to the center of mass of the
15 moderately hydrophobic moiety in the P4 binding
pocket is between about 14Å and about 22Å.

20 13. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P2 binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P2 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
25 pocket is between about 5.5Å and about 13Å.

30 14. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P2 binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety

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in the P2 binding pocket to the center of mass of the moderately hydrophobic moiety in the P4 binding pocket is between about 9Å and about 17Å.

5 15. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P3 binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
10 in the P3 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P4 binding
pocket is between about 7.5Å and about 17Å.

15 16. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Arg-341 of ICE and
wherein the distance between said hydrogen bonding
20 moieties is between about 5Å and about 7.5Å.

25 17. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the amide -NH- group of Arg-341 of ICE and
wherein the distance between said moieties is between
about 2.5Å and about 5Å.

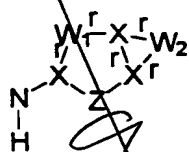
30 18. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,

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said first hydrogen bonding moiety forms a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE and said second hydrogen bonding moiety forms a hydrogen bond with the amide -NH- group of Arg-341 of ICE and wherein the distance between said hydrogen bonding moieties is between about 2.5Å and about 4Å.

19. An ICE inhibitor comprising:
(a) a scaffold of formula I:

(I)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₁ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

W₂ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen

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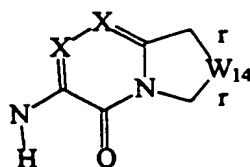
bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

20. The ICE inhibitor according to claim 19, wherein said scaffold has the formula:

(IA)



wherein:

each X is independently C or N;

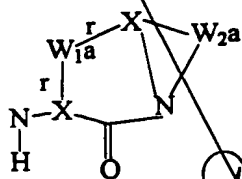
W₁₄ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or

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unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and
each bond labeled r is independently a single or a double bond.

21. The ICE inhibitor according to claim 19, wherein said scaffold has the formula:

(IB)



wherein:

X is C or N;

W_{1a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

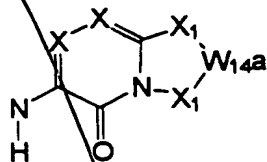
W_{2a} is a straight chain comprising 3-4 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different atoms to form an aryl or heteroaromatic ring therewith; and

each bond labeled r is independently a single or a double bond.

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22. The ICE inhibitor according to claim 19,
wherein said scaffold has the formula:

(IC)

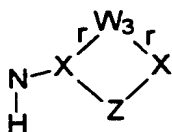


wherein:

- 5 each X is independently C or N;
 each X₁ is independently C, N, or O; and
 W_{14a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
10 bonds between said members being saturated or
unsaturated and said chain comprising two ends which
are covalently bound to two different X₁ atoms to
form a non-aromatic ring therewith.

23. An ICE inhibitor comprising:
a scaffold of formula II:

(II)



wherein:

- each X is independently C or N;
 Z is CO or SO₂;
20 W₃ is a straight chain comprising 2-4
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
25 two ends which are covalently bound to two different
X atoms through bonds r;
 each bond labeled r is independently a
single or a double bond;

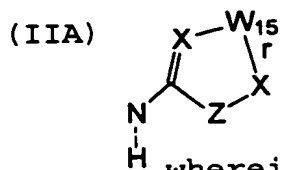
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H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(a) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(b) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

24. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:



each X is independently C or N;
Z is CO or SO₂;

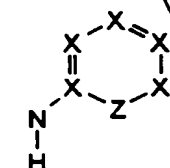
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W₁₅ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

25. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIB)

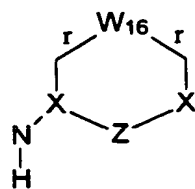


wherein:

each X is independently C or N; and
Z is CO or SO₂.

26. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIC)



wherein:

each X is independently C or N;
Z is CO or SO₂;

W₁₆ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising

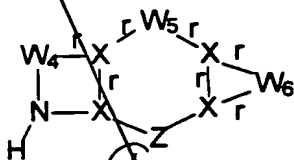
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two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

- 5 27. An ICE inhibitor comprising:
 (a) a scaffold of formula III:

(III)



, wherein:

10 each X is independently C or N;

 Z is CO or SO₂;

 W₄ is a straight chain comprising 2-4 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

 W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

 W₆ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

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each bond labeled r is independently a single or a double bond;

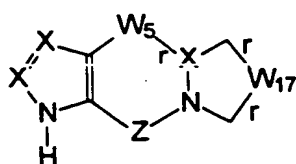
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

28. The ICE inhibitor according to claim 27, wherein said scaffold has the formula:

(IIIA)



wherein:

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each X is independently C or N;

Z is CO or SO₂;

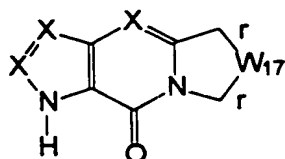
W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

W₁₇ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

29. The ICE inhibitor according to claim 27,

wherein:
(IIIB)



wherein:

each X is independently C or N;

W₁₇ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a

single or a double bond.

30. An ICE inhibitor comprising:

(a) a scaffold of formula IV:

(IV)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₇ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

W₈ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated, and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide

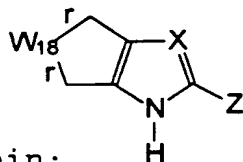
-NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

31. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVA)



wherein:

each X is independently C or N;

Z is CO or SO₂;

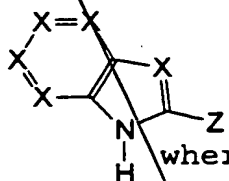
W₁₈ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a

single or a double bond.

32. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVB)

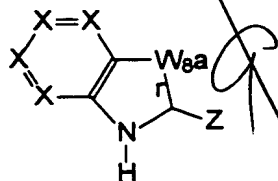


wherein:

each X is independently C or N; and
Z is CO or SO₂.

33. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVC)



wherein:

each X is independently C or N;
Z is CO or SO₂;

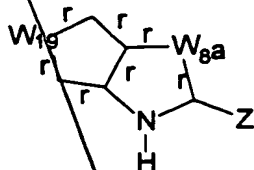
W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms; and

the bond labeled r is a single or a double bond.

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34. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

(IVD)



wherein:

Z is CO or SO₂;

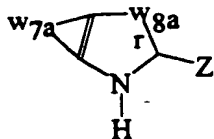
W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r;

W₁₉ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

35. The ICE inhibitor according to claim 30,
wherein said scaffold has the formula:

(IVE)



wherein:

Z is CO or SO₂;

W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from

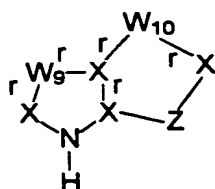
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the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms;

5 W_7 is a straight chain comprising 3 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different C atoms to form an aryl ring therewith; and
10 the bond labeled r is a single or a double bond.

36. An ICE inhibitor comprising:
a) a scaffold of formula V:

15 (V)



wherein:

each X is independently C or N;

Z is CO or SO₂;

20 W_9 is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising
25 two ends which are covalently bound to two different X atoms through bonds r;

W_{10} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent
30 bonds between said members being independently saturated or unsaturated and said chain comprising

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two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

5 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the
10 carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

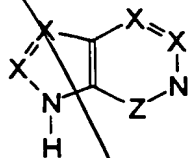
b) a first and a second moderately
15 hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group
20 consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

c) an electronegative moiety comprising
25 one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

30 37. The ICE inhibitor according to claim 36, wherein said scaffold has the formula:

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(VA)

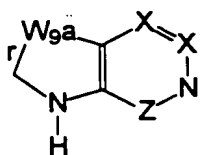


wherein:

each X is independently C or N; and
Z is CO or SO₂.

38. The ICE inhibitor according to claim 36,
wherein said scaffold has the formula:

(VB)



wherein:

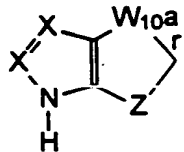
each X is independently C or N;
Z is CO or SO₂;

W_{9a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
C atoms; and

the bond labeled r is a single or a
double bond.

39. The ICE inhibitor according to claim 36,
wherein said scaffold has the formula:

(VC)



wherein:

each X is independently C or N;

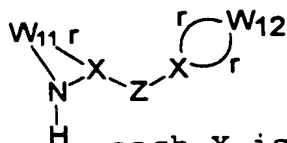
Z is CO or SO₂;

W_{10a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

40. An ICE inhibitor comprising:
(a) a scaffold of formula VI:

(VI)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₁₁ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms to form a ring which may optionally be benzofused or pyridinofused;

W₁₂ is a straight chain comprising 4-6 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to the indicated X atom through bonds r;

each bond labeled r is independently a

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single or a double bond;

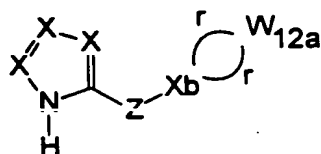
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

41. The ICE inhibitor according to claim 40, wherein said scaffold has the formula:

(VIA)



wherein:

each X and X_b is independently C or N;

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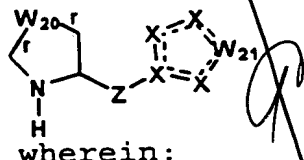
Z is CO or SO₂;

W_{12a} is a straight chain comprising 4-6 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to the indicated X_b atom through bonds r; and

each bond labeled r is independently a single or a double bond.

42. The ICE inhibitor according to claim 40, wherein said scaffold has the formula:

(VIB)



wherein:

each X is independently C or N;

Z is CO or SO₂;

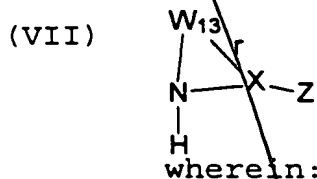
W₂₀ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r;

W₂₁ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different C atoms to form an aryl ring therewith; and

each bond labeled r is independently a single or a double bond.

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43. An ICE inhibitor comprising:
(a) a scaffold of formula VII:



5 X is C or N;

Z is CO or SO₂;

W₁₃ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

10 the bond labeled r is a single or a double bond;

15 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

20 (b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

25

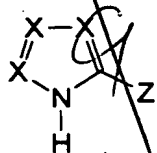
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(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

44. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

(VIIA)

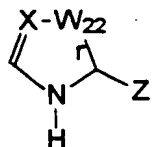


wherein:

each X is independently C or N; and
Z is CO or SO₂.

45. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

(VIIB)



wherein:

X is C or N;
Z is CO or SO₂;

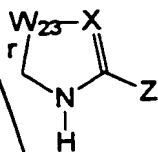
W₂₂ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

the bond labeled r is a single or a double bond.

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46. The ICE inhibitor according to claim 43,
wherein said scaffold has the formula:

(VIIC)



wherein:

X is C or N;

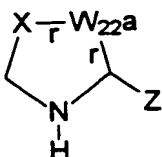
Z is CO or SO₂;

W₂₃ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

the bond labeled r is a single or a double bond.

47. The ICE inhibitor according to claim 43,
wherein said scaffold has the formula:

(VIID)



wherein:

X is C or N;

Z is CO or SO₂;

W_{22a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

48. An ICE inhibitor comprising:

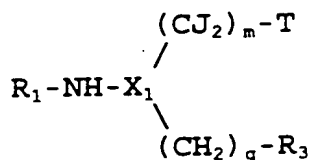
- 5 a) a scaffold comprising any monocyclic, bicyclic or tricyclic system, wherein each ring of said system comprises 5-7 members, said system comprising C, N, O or S, said system being aromatic or non-aromatic and comprising a central ring, wherein the distance between the centroid of
10 said central ring and the alpha carbon of Cys-285 of ICE is between about 5.0Å and about 6.0Å when the inhibitor is bound to ICE and the distance between the centroid of said central ring and the alpha carbon of His-237 of ICE is between about 5.5Å and
15 about 6.5Å when the inhibitor is bound to ICE;
- b) a first hydrogen bonding moiety and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said atoms
20 being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;
- c) a first and a second moderately
25 hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group
30 consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

d) an electronegative moiety

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comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

49. A compound represented by the formula:



wherein:

X_1 is CH or N;

g is 0 or 1;

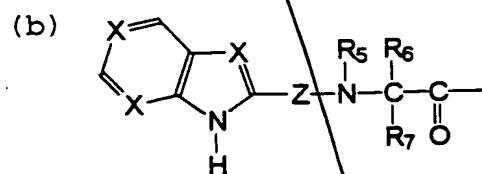
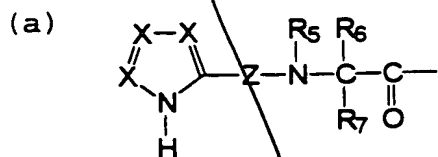
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

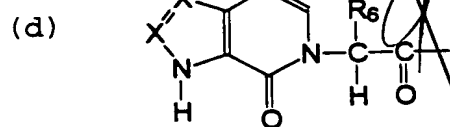
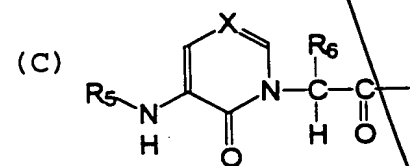
T is -Ar₃, -OH, -CF₃, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H;

R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or halogen, and in which any saturated ring may optionally be unsaturated at one or two bonds:

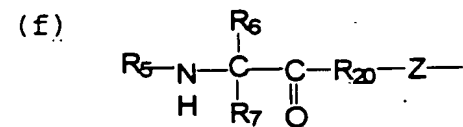
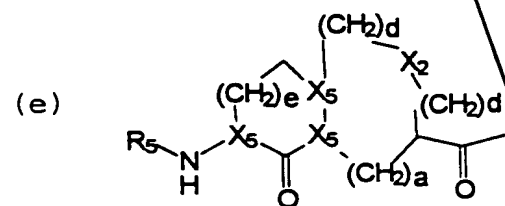
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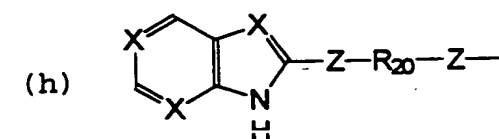
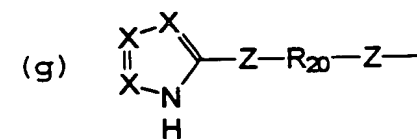
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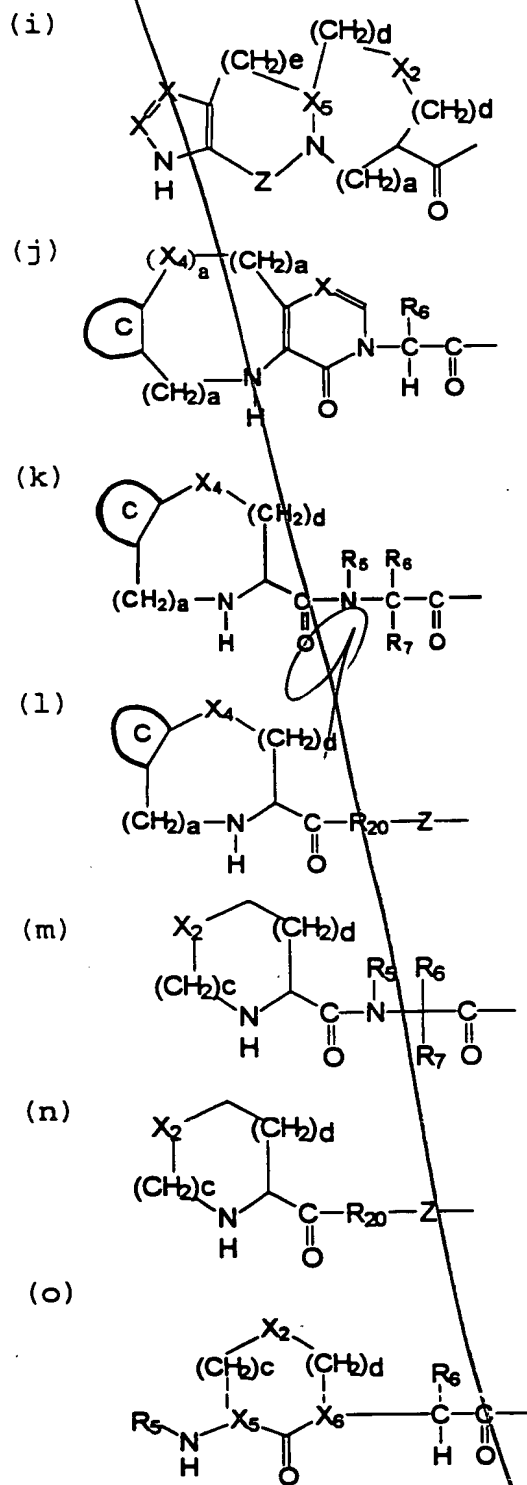


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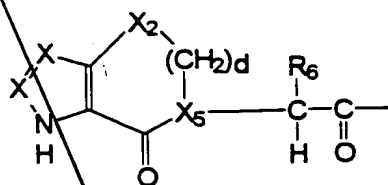
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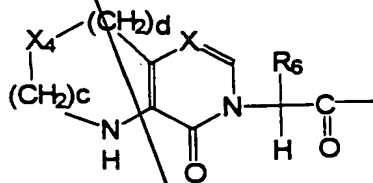


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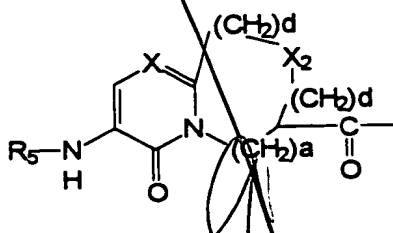
(p)



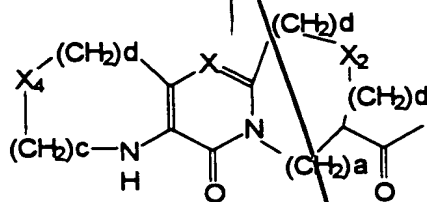
(q)



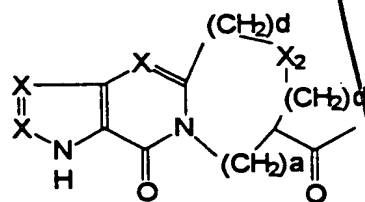
(r)



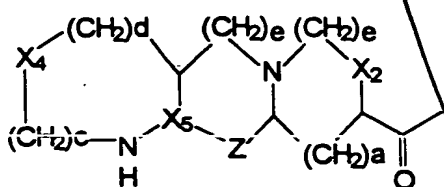
(s)



(t)



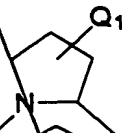
(v)



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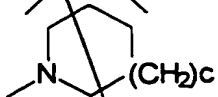
R_{20} is selected from the group consisting of:

(aa1)



;

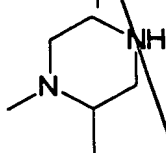
(aa2)



;

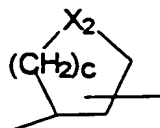
5

(aa3)



;

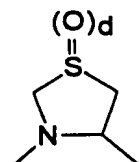
(aa4)



;

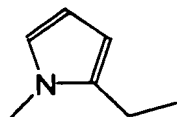
10

(aa5)



;

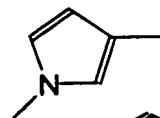
(bb)



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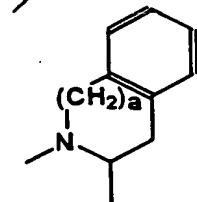
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(cc)



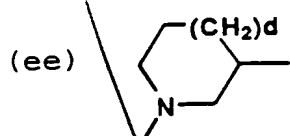
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(dd)

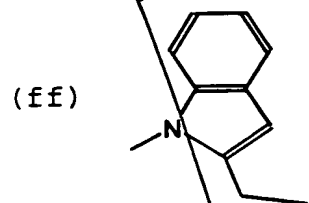


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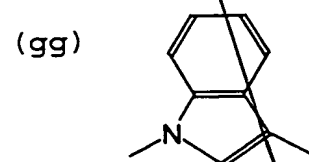
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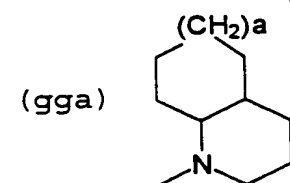
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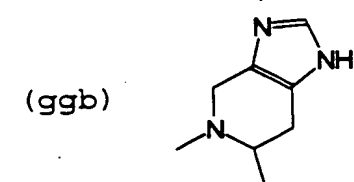
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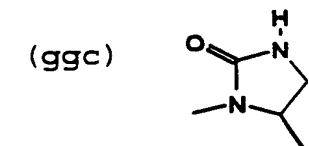
;



;



;



; and

20 wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

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R_3 is

-CN,

-CH=CH- R_9 ,

-CH=N-O- R_9 ,

5 - (CH₂)₁₋₃-T₁- R_9 ,

-CJ₂- R_9 ,

-CO- R_{13} , or

/ R_5

10 -CO-CO-N R_{10} ;

each R_4 is independently selected from the group consisting of:

-H,

-Ar₁,

15 - R_9 ,

-T₁- R_9 , and

-(CH₂)_{1,2,3}-T₁- R_9 ,

each T₁ is independently selected from the group consisting of:

20 -CH=CH-,

-O-,

-S-,

-SO-,

-SO₂-,

25 -NR₁₀-,

-NR₁₀-CO-,

-CO-,

-O-CO-,

-CO-O-,

30 -CO-NR₁₀-,

-O-CO-NR₁₀-,

-NR₁₀-CO-O-,

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-NR₁₀-CO-NR₁₀- ,
 -SO₂-NR₁₀- ,
 -NR₁₀-SO₂- , and
 -NR₁₀-SO₂-NR₁₀- ,

5 each R₅ is independently selected from the group
 consisting of:

-H,
 -Ar₁,
 -CO-Ar₁,
 10 -SO₂-Ar₁,
 -R₉,
 -CO-R₉,
 -CO-O-R₉,
 -SO₂-R₉,
 15 -CO-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,
 -SO₂-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,
 20 -CO-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$, and
 25 -SO₂-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$,

R₆ and R₇ taken together form a saturated 4-8
 member carbocyclic ring or heterocyclic ring
 30 containing -O-, -S-, or -NH-, or R₇ is -H and R₆ is

-H
 -Ar₁,

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-R₉, or
- (CH₂)_{1,2,3}-T₁-R₉,

5 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

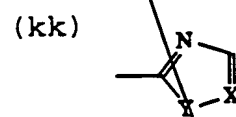
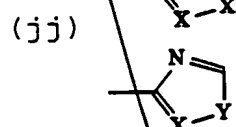
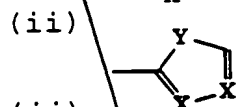
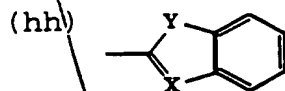
each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

10 each R₁₁ is independently selected from the group consisting of -Ar₂ and -R₄,

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15 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3
20 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic
25 rings, and said cyclic group optionally being singly or multiply substituted by =O, -OH, perfluoro C₁₋₃ alkyl, or -Q₁;

each Ar₂ is independently selected from the following group, in which any ring may optionally be

substituted by $-Q_1$:



, and

;

Ar_3 is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $=N-$, and $-NH-$, said cyclic group optionally being singly or multiply substituted with $=O$, $-OH$, halogen, perfluoro C_{1-3} alkyl, or $-CO_2H$;

each Q_1 is independently selected from the group consisting of

- $-Ar_1$
- $-R_9$,
- $-T_1-R_9$, and
- $-(CH_2)_{1,2,3}-T_1-R_9$,

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

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each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

5 each X_3 is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X_4 is independently selected from the group consisting of -CH₂- and -NH-;

10 each X_5 is independently selected from the group consisting of -CH- and -N-;

X_6 is CH or N, provided that when X_6 is N in the R_1 group labeled (o) and X_5 is CH and X_2 is CH₂ the ring of the R_1 group labeled (o) must be substituted by Q_1 or benzofused;

15 each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO₂,

each a is independently 0 or 1,

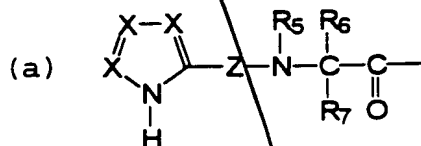
20 each c is independently 1 or 2,

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

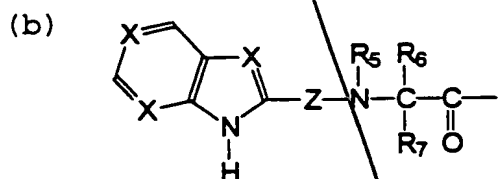
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50. The compound according to claims 49 or 80, wherein R_1 is:



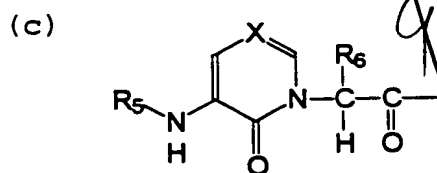
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51. The compound according to claims 49 or 80, wherein R_1 is:



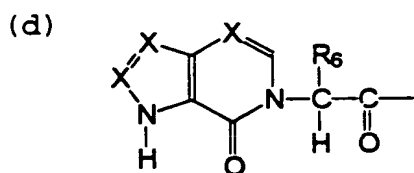
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52. The compound according to claims 49 or 80, wherein R_1 is:



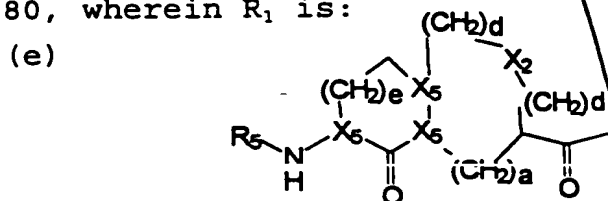
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53. The compound according to claims 49 or 80, wherein R_1 is:



20

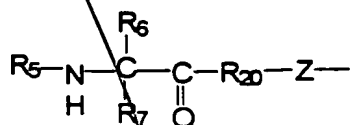
54. The compound according to claims 49 or 80, wherein R_1 is:



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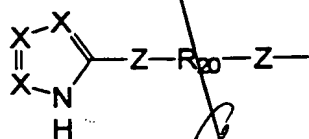
55. The compound according to claims 49 or 80, wherein R_1 is:

(f)



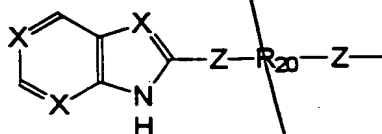
56. The compound according to claims 49 or 80, wherein R_1 is:

(g)



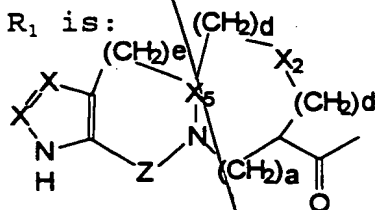
57. The compound according to claims 49 or 80, wherein R_1 is:

(h)



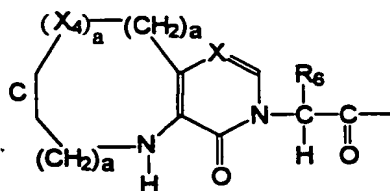
58. The compound according to claims 49 or 80, wherein R_1 is:

(i)



59. The compound according to claims 49 or 80, wherein R_1 is:

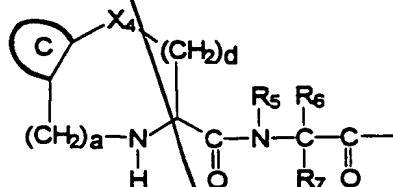
(j)



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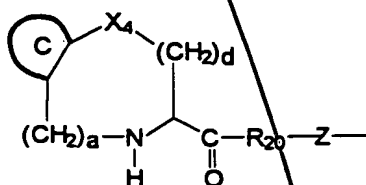
60. The compound according to claims 49 or 80, wherein R_1 is:

(k)



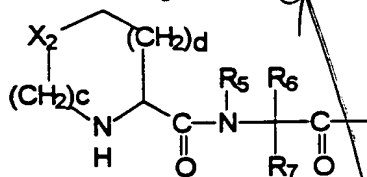
61. The compound according to claims 49 or 80, wherein R_1 is:

(l)



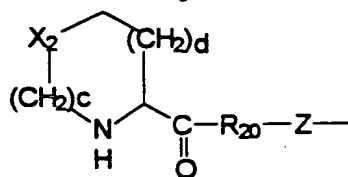
62. The compound according to claims 49 or 80, wherein R_1 is:

(m)



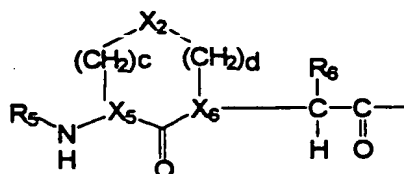
63. The compound according to claims 49 or 80, wherein R_1 is:

(n)



64. The compound according to claims 49 or 80, wherein R_1 is:

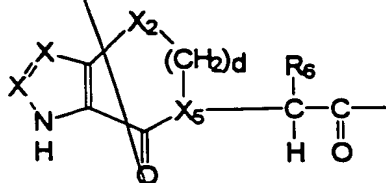
(o)



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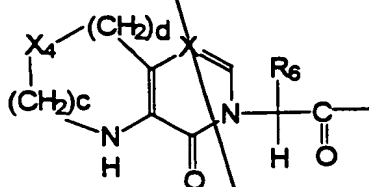
65. The compound according to claims 49 or 80, wherein R_1 is:

(p)



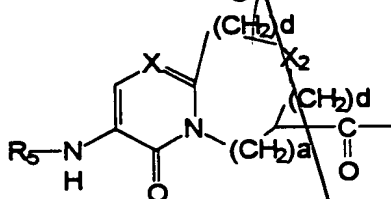
66. The compound according to claims 49 or 80, wherein R_1 is:

(q)



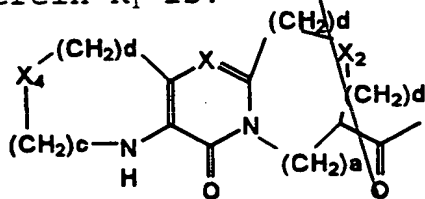
67. The compound according to claims 49 or 80, wherein R_1 is:

(r)



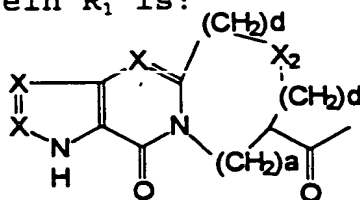
68. The compound according to claims 49 or 80, wherein R_1 is:

(s)



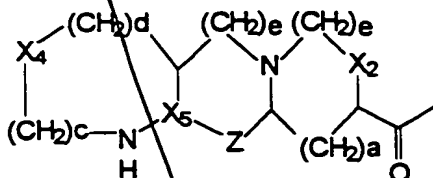
69. The compound according to claims 49 or 80, wherein R_1 is:

(t)



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70. The compound according to claims 49 or 80, wherein R_1 is:
(v)



5

71. A pharmaceutical composition for treating or preventing an IL-1 mediated disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

10

72. A pharmaceutical composition for treating or preventing an autoimmune disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

15

73. A pharmaceutical composition for treating or preventing an inflammatory disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of 1-70 and 80-124 and a pharmaceutically acceptable carrier.

20

74. A pharmaceutical composition for treating or preventing a neurodegenerative disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

25

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75. A pharmaceutical composition for inhibiting an ICE-mediated function comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

5

76. A method for treating or preventing a disease selected from the group consisting of IL-1 mediated disease, autoimmune disease, inflammatory disease and neurodegenerative disease in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 71 to 75.

77. A method for selecting an ICE inhibitor comprising the steps of:

15

a) selecting a candidate compound of defined chemical structure comprising at least two hydrogen bonding moieties, at least two moderately hydrophobic moieties and one electronegative moiety comprising one or more electronegative atoms attached either to the same atom or to adjacent atoms in the electronegative moiety;

20

b) determining a low-energy conformation for binding of said compound to the active site of ICE;

25

c) evaluating the capability of said compound in said conformation to form at least two hydrogen bonds with the non-carbon backbone atoms of Arg-341 and Ser-339 of ICE;

30

d) evaluating the capability of said compound in said conformation to associate with at least two of the binding pockets of ICE selected from the group consisting of the P2 binding pocket, the P3

binding pocket, the P4 binding pocket and the P' binding pocket;

5 e) evaluating the capability of said compound in said conformation to interact with the P1 binding pocket of ICE; and

f) accepting or rejecting said candidate compound as an ICE inhibitor based on the determinations and evaluations carried out in the preceeding steps.

10 78. The method of claim 77, additionally comprising the following steps which follow step e) and preceed step f):

g) evaluating the deformation energy of binding of said compound to ICE; and

15 h) evaluating the contribution of the sum of all electrostatic interactions between said compound and ICE when said compound is bound thereto in said conformation.

20 79. An ICE inhibitor selected by either of the methods according to ~~claims~~ 77 or 78.

80. A compound represented by the formula:



wherein:

X₁ is -CH;

30 g is 0 or 1;

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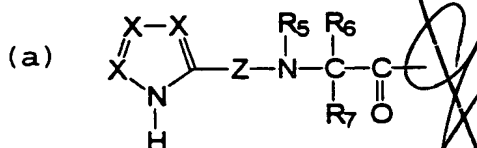
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

5 m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric replacement for -CO₂H;

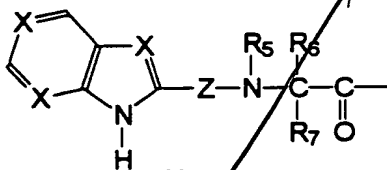
10 R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein R₁ (e) and R₁ (y) are optionally benzofused;

15



;

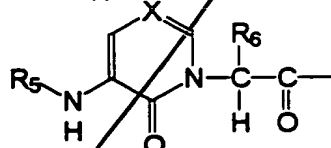
(b)



;

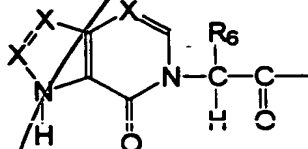
20

(c)



;

(d)

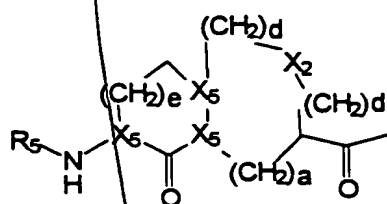


;

25

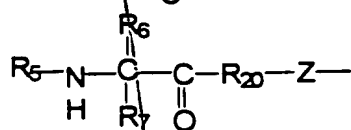
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(e)



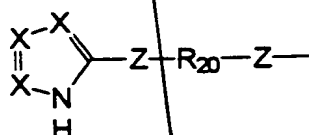
i

(f)



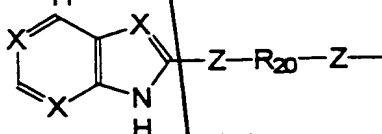
i

(g)



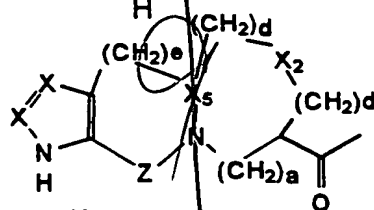
i

(h)



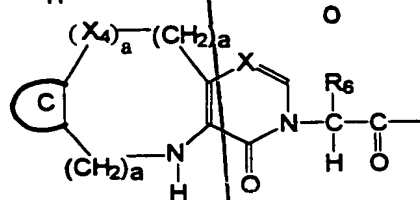
i

(i)



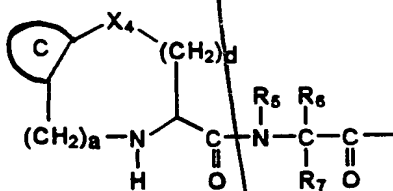
i

(j)



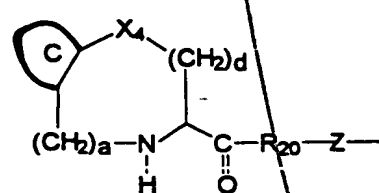
i

(k)



i

(l)

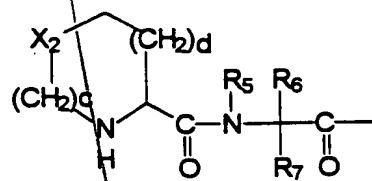


i

25

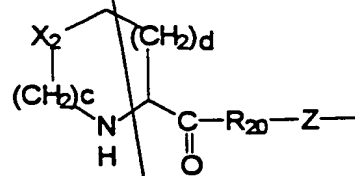
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(m)



;

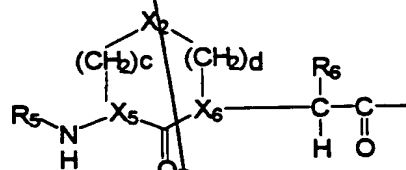
(n)



5

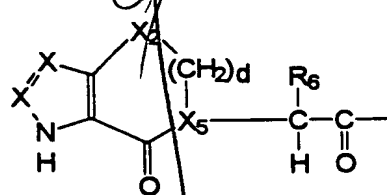
;

(o)



;

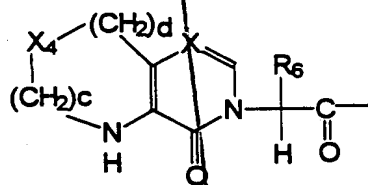
(p)



10

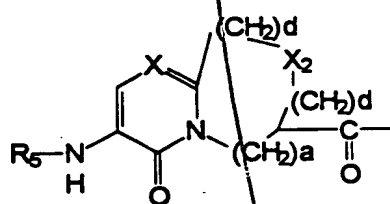
;

(q)



;

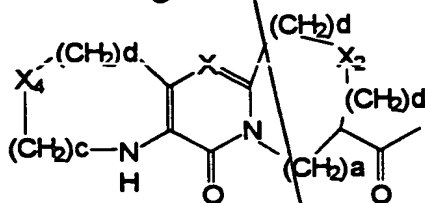
(r)



15

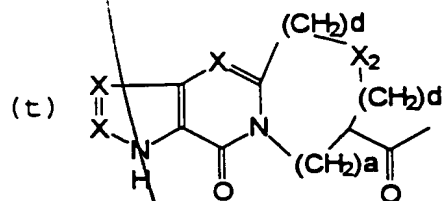
;

(s)



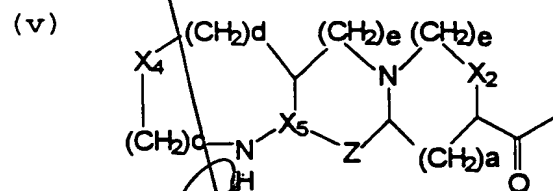
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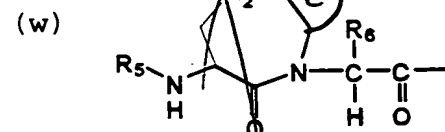


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5

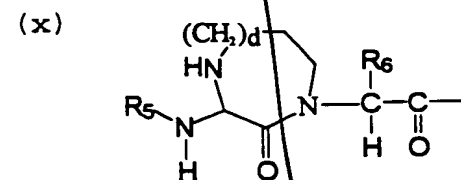


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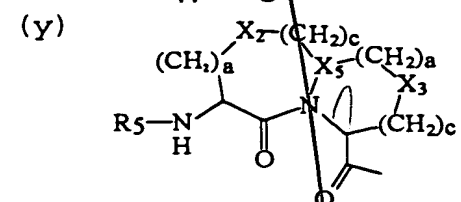


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10



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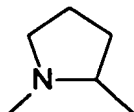


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15

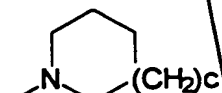
R₂₀ is selected from the group consisting of:

(aa1)



;

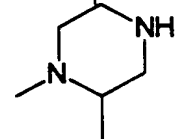
(aa2)



;

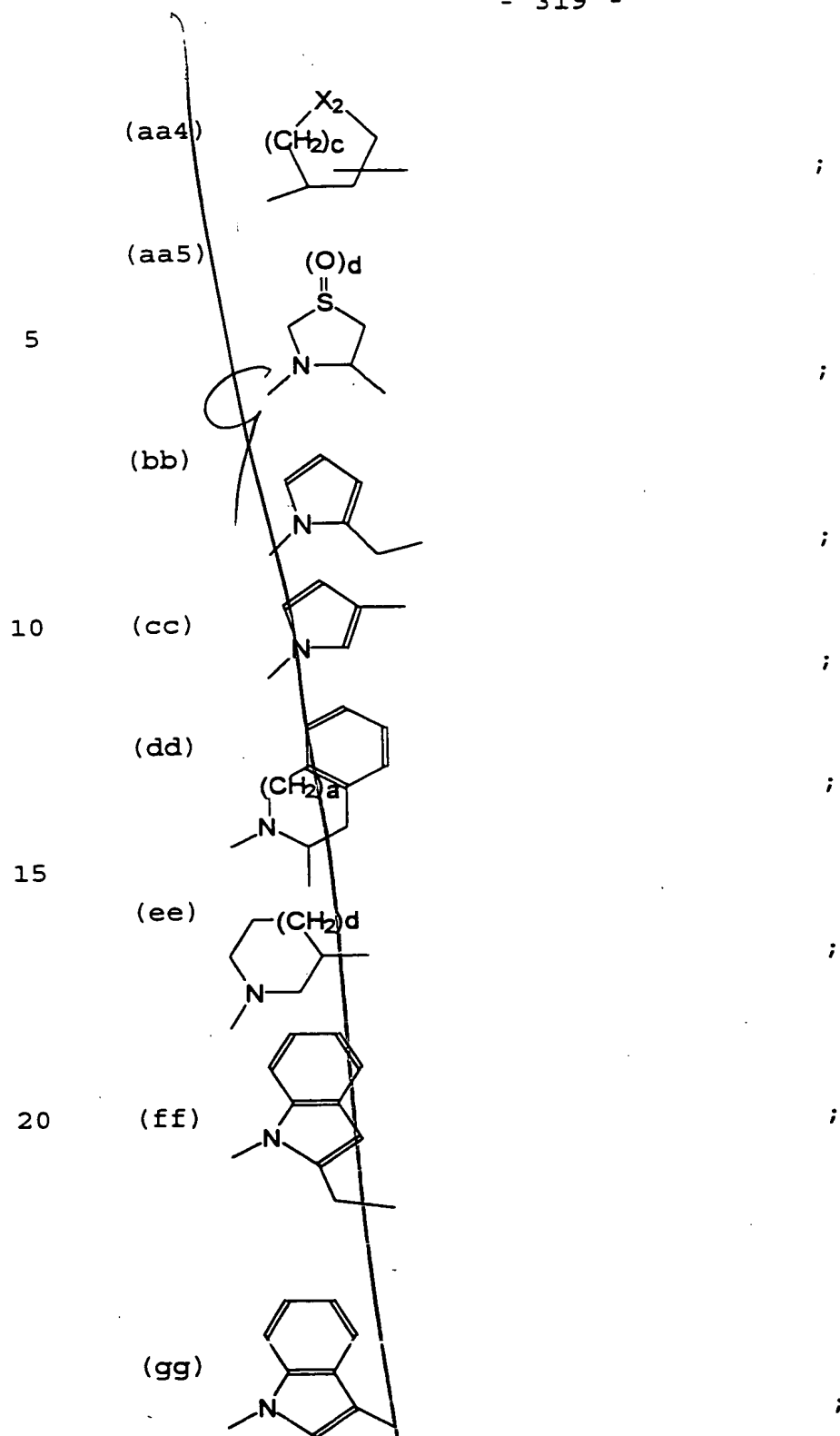
20

(aa3)

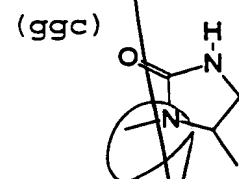
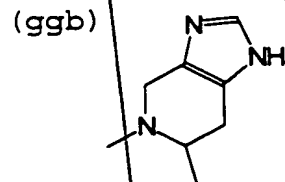
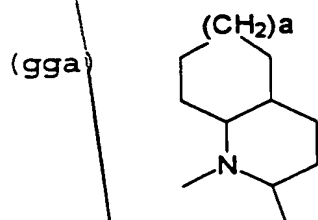


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wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:

- CN,
- CH=CH- R_9 ,
- CH=N-O- R_9 ,
- 20 - $(CH_2)_{1-3}$ - T_1 - R_9 ,
- CJ₂- R_9 ,
- CO- R_{13} , or
- CO-CO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;

each R_4 is independently selected from the group consisting of:

- H,
- Ar₁,

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$$-T_1 - R_9, \text{ and}$$
$$-(\text{CH}_2)_{1,2,3}-\text{T}_1-\text{R}_9;$$

5

$$\text{CH}=\text{CH}-,$$

-6-

LS

-SOI,

$$-\text{SO}_2-$$

-NR₁₀-

$$-\text{NR}_{10}-\text{CO}-,$$

-CO-

$$-\text{O}-\text{CO}-$$
$$-\text{CO}-\text{O}-,$$
$$-\text{CO}-\text{NR}_{10}-,$$
$$-O-CO-NR_{10}-,$$
$$-\text{NR}_{10}-\text{CO}-\text{O}-,$$
$$-\text{NR}_{10}-\text{CO}-\text{NR}_{10}-,$$
$$-\text{SO}_2-\text{NR}_{10}-,$$
$$-\text{NR}_{10}-\text{SO}_2-, \quad \text{and}$$
$$-\text{NR}_{10}-\text{SO}_2-\text{NR}_{10}-;$$

consisting of:

-H,

-Ar₁,

$$-\text{CO}-\text{Ar}_1,$$
$$-\text{SO}_2-\text{Ar}_1,$$
$$-\text{CO}-\text{NH}_2$$
$$-\text{SO}_2-\text{NH}_2,$$

-R₉,

$$-\text{CO}-\text{R}_9,$$

$$-\text{SO}_2-\text{R}_9,$$
$$-\text{CO}-\text{N} \begin{array}{l} \diagup \\ \diagdown \end{array} \text{R}_{10},$$
$$-\text{SO}_2-\text{N} \begin{array}{l} \diagup \text{Ar}_1 \\ \diagdown \text{R}_{10}, \end{array}$$
$$-\text{CO}-\text{N} \begin{array}{l} \diagup \text{R}_9 \\ \diagdown \text{R}_{10} \end{array}$$
$$-\text{SO}_2-\text{N} \begin{array}{l} / \text{R}_9 \\ \backslash \text{R}_{10}; \end{array}$$

R₆ and R₇ taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R₇ is -H and R₆ is

-Ar,

$$-(\text{CH}_2)_{1,2,3}-\text{T}_1-\text{R}_2, \text{ or}$$

an α -amino acid side chain residue;

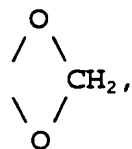
each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

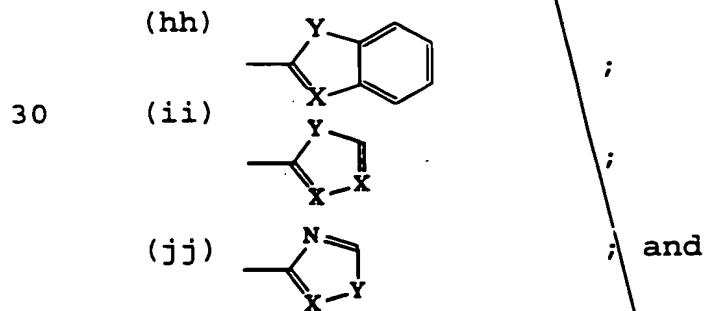
each R_{13} is independently selected from the group

consisting of $-Ar_2$, $-R_4$ and $-N-OH$
 R_5 ;

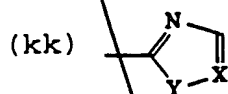
each Ar_1 is a cyclic group independently selected
 5 from the set consisting of an aryl group which
 contains 6, 10, 12, or 14 carbon atoms and between 1
 and 3 rings, a cycloalkyl group which contains
 between 3 and 15 carbon atoms and between 1 and 3
 rings, said cycloalkyl group being optionally
 10 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 heteroatom group selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$,
 $=N-$, and $-NH-$, said heterocycle group optionally
 15 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 or multiply substituted by $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$,
 $-I$, $-NO_2$, $-CN$,

20 $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$,  or $-Q_1$;

25 each Ar_2 is independently selected from the
 following group, in which any ring may optionally be
 singly or multiply substituted by $-Q_1$ and $-Q_2$:



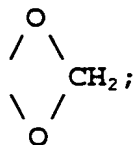
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each Q_1 is independently selected from the group consisting of:

- Ar₁
- O-Ar₁
- R₉,
- T₁-R₉, and
- (CH₂)_{1,2,3}-T₁-R₉;

each Q_2 is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, -CF₃, and



provided that when -Ar₁ is substituted with a Q_1 group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q_1 ;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X_3 is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X_4 is independently selected from the group consisting of -CH₂- and -NH-;

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each X_5 is independently selected from the group
consisting of $-\text{CH}-$ and $-\text{N}-$;

X_6 is $-\text{CH}-$ or $-\text{N}-$;

5 each Y is independently selected from the group
consisting of $-\text{O}-$, $-\text{S}-$, and $-\text{NH}$;

each Z is independently CO or SO_2 ;

each a is independently 0 or 1;

each c is independently 1 or 2;

10 each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

15 R_1 is (f),
 R_6 is an α -amino acid side chain residue, and
 R_7 is $-\text{H}$,
then (aa1) and (aa2) must be substituted with Q_1 ;

also provided that when

20 R_1 is (o),
 g is 0,
 J is $-\text{H}$,
 m is 1,
 R_6 is an α -amino acid side chain residue,
25 R_7 is $-\text{H}$,
 X_2 is $-\text{CH}_2-$,
 X_5 is $-\text{CH}-$,

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X₆ is -N- , and
|

R₃ is $\begin{array}{l} \text{---} / R_{10} \\ \text{---CO-N} \\ \text{---} \backslash R_{10} \end{array}$, or -CO-R₁₃, when

R₁₃ is:

-CH₂-O-CO-Ar₁,

-CH₂-S-CO-Ar₁,

-CH₂-O-Ar₁,

-CH₂-S-Ar₁, or

-R₄ when -R₄ is -H;

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

R₁ is (w),

g is 0,

J is -H,

m is 1,

T is -CO₂H,

X₂ is O,

R₅ is benzyloxycarbonyl, and

ring C is benzo,

then R₃ cannot be -CO-R₁₃ when:

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

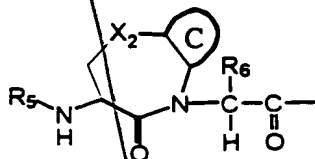
R₁₃ is -CH₂-O-CO-Ar₁, wherein

Ar₁ is 2,6-dichlorophenyl.

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81. The compound according to claim 80,
wherein R_1 is:

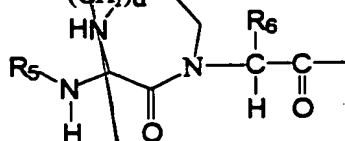
(w)



5

82. The compound according to claim 80,
wherein R_1 is:

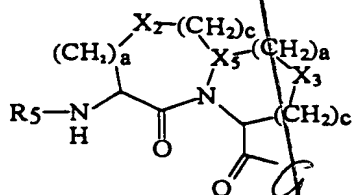
(x)



10

83. The compound according to claim 80,
wherein R_1 is:

(y)



15

84. The compound according to claim 80,
wherein:

X_1 is $-CH$;

g is 0;

20

J is $-H$;

m is 0 or 1 and T is $-CO-CO_2H$, or any bioisosteric
replacement for $-CO_2H$, or

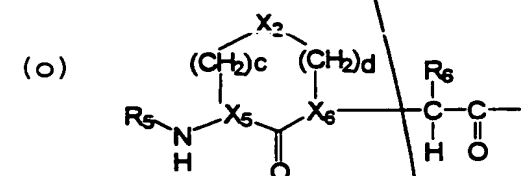
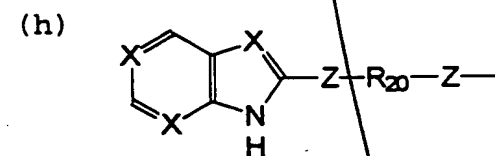
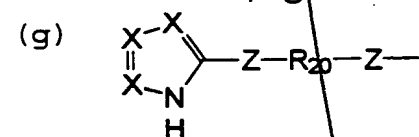
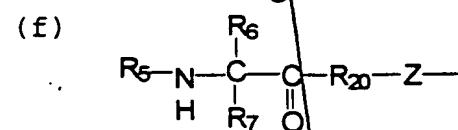
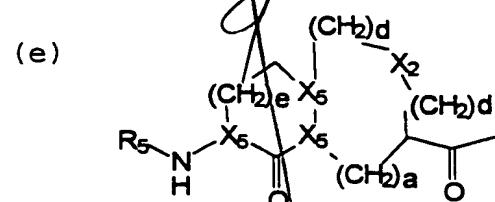
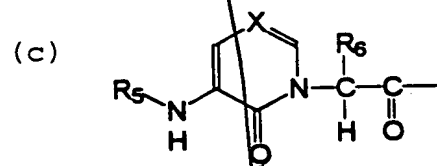
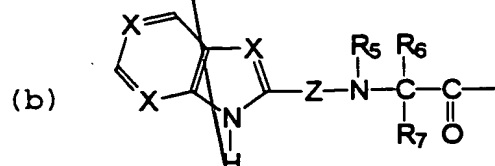
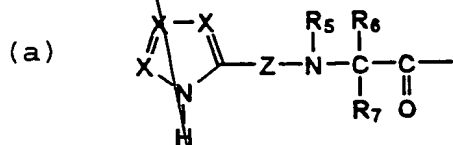
m is 1 and T is $-CO_2H$;

R_1 is selected from the group consisting of the
following formulae, in which any ring may optionally
be singly or multiply substituted at any carbon by

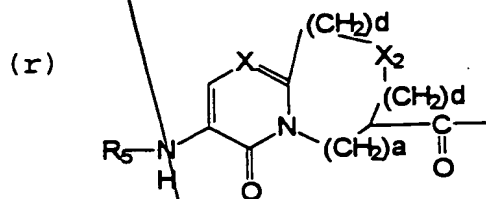
25

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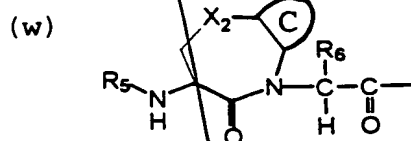
Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:



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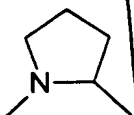
, or



;

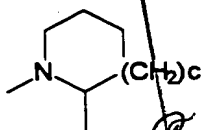
R₂₀ is:

(aa1)



, or

(aa2)



and c is 1;

ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;

when R₁ is (a) or (b), R₅ is preferably -H, and

when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:

- CO-Ar₁
- SO₂-Ar₁,
- CO-NH₂,
- CO-NH-Ar₁
- CO-R₉,
- CO-O-R₉,

~~-SO₂-R₉, or~~

~~-CO-NH-R₉,~~

~~R₇ is -H and R₆ is: -H,~~

~~-R₉, or~~

~~-Ar₁;~~

5

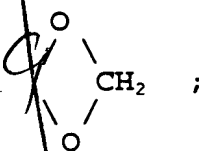
~~R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar₁;~~

10

~~R₁₀ is -H or a -C₁₋₃ straight or branched alkyl group;~~

~~Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl substituted with -O-C₁₋₃ alkyl, -NH-C₁₋₃ alkyl, -N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃, -C₁₋₃ alkyl, or~~

15



20

~~Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein T₁ is -O- or -S-;~~

~~each X is independently selected from the group consisting of =N-, and° =CH-;~~

25

~~each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;~~

~~each X₅ is independently selected from the group consisting of -CH- and -N-;~~



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X_6 is $-\text{CH}-$ or $-\text{N}-$,

provided that when:

R_1 is $R_1(\text{O})$,

5 X_2 is $-\text{CH}_2-$,

X_3 is $-\text{CH}-$, and

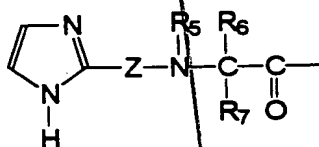
10 X_6 is $-\text{N}-$,

then the ring of the $R_1(\text{O})$ group must be substituted with Q_1 or benzofused; and

Z is $\text{C}=\text{O}$.

15 85. The compound according to claim 84, wherein the R_1 group is

(a2)



optionally substituted with Q_1 , wherein

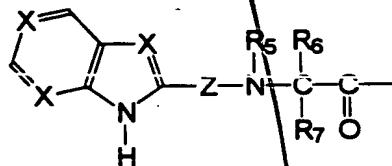
20 R_5 is $-\text{H}$;

R_7 is $-\text{H}$; and

Z is $\text{C}=\text{O}$.

86. The compound according to claim 84, wherein the R_1 group is

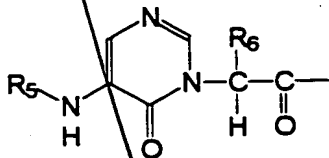
(b)



optionally substituted with Q_1 , wherein

R_5 is -H;
 R_7 is -H; and
 Z is C=O.

87. The compound according to claim 84,
wherein the R_1 group is
(c1)



which is optionally substituted with Q_1 ;

provided that when R_1 is (c1),

g is 0,

J is -H,

m is 1,

T is $-CO_2H$,

X is N,

R_5 is benzyloxycarbonyl, and

R_6 is -H,

then R_3 cannot be $-CO-R_{13}$ when

R_{13} is $-CH_2-O-Ar_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom; or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein

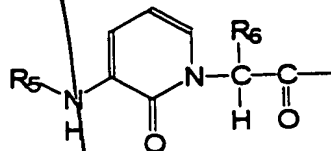
Ar_1 is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl.

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88. The compound according to claim 84,
wherein the R_1 group is:

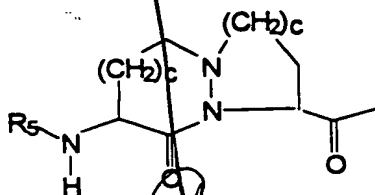
(c2)



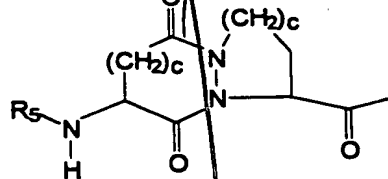
which is optionally substituted with Q_1 .

89. The compound according to claim 84,
wherein the R_1 group is:

(e1)

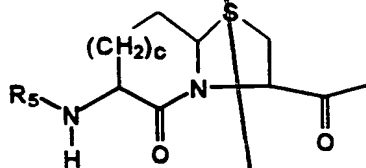


(e2)

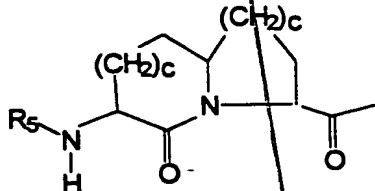


and c is 2; or

(e4)



(e7)



which is optionally benzofused,
and c is 1 or 2;

provided that when R_1 is (e4),

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g is 0,
J is -H,
m is 1,
T is -CO₂H,
5 R₅ is benzyloxycarbonyl, and
c is 1,

then R₃ cannot be -CO-R₁₃ when
R₁₃ is -CH₂-O-Ar₁ and
Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-
10 5-yl, wherein the phenyl is optionally substituted
with a chlorine atom; or when

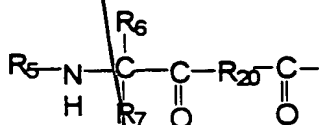
R₁₃ is -CH₂-O-CO-Ar₁, wherein
Ar₁ is 2,6-dichlorophenyl,
15 and when the 2-position of the scaffold ring is
substituted with para-fluoro-phenyl; and

also provided that when
R₁ is (e7),
g is 0,
20 J is -H,
m is 1,
T is -CO₂H or -CO-NH-OH,
R₅ is a protective group for the N atom of an
amino acid side chain residue, and
25 each c is 1,

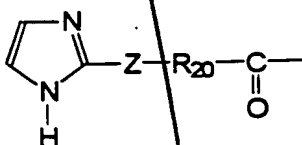
then R₃ cannot be -CO-R₁₃ when
R₁₃ is:
-CH₂-O-CO-Ar₁,
-CH₂-S-CO-Ar₁,
30 -CH₂-O-Ar₁, or
-CH₂-S-Ar₁.

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90. The compound according to claim 84,
wherein the R_1 group is
(f1)



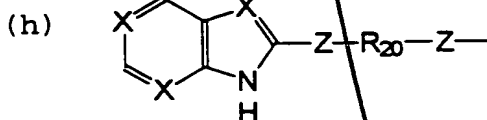
91. The compound according to claim 84,
wherein the R_1 group is
(g2)



, wherein
 R_{20} is (aa1) optionally substituted singly or
multiply with Q_1 ; and

Z is C=O.

92. The compound according to claim 84,
wherein the R_1 group is



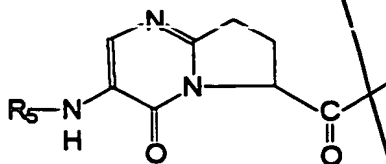
, wherein

R_{20} is (aa1) optionally substituted singly or
multiply with Q_1 ; and

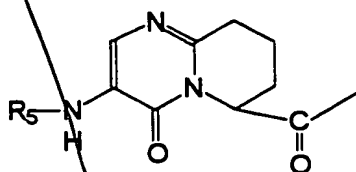
Z is C=O.

93. The compound according to claim 84,
wherein the R_1 group is:

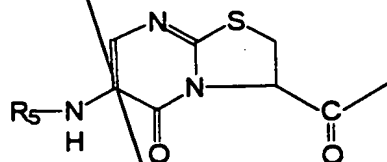
(r3)



(r4)



(r5)

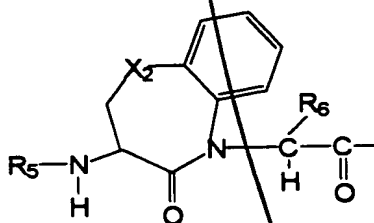


optionally substituted with Q₁.

5

94. The compound according to claim 84,
wherein the R₁ group is

(w1)



; wherein

X₂ is:

10

-O- ,
-S- ,
-SO₂-, or
-NH-;

15

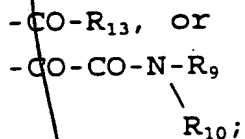
optionally substituted with R₅ or Q₁ at X₂ when X₂
is -NH-; and

ring C is benzo substituted with -C₁₋₃ alkyl,
-O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

20

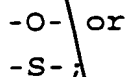
95. The compound according to claim 84,
wherein

R₃ is:



5

T₁ is:

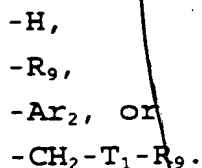


10

R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with Ar₁; and

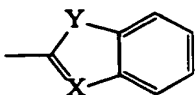
R₁₃ is:

15



96. The compound according to claim 95, wherein -Ar₂ is:

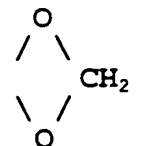
(hh)



20

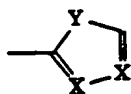
optionally substituted singly or multiply with -C₁₋₆ alkyl, -O-C₁₋₆ alkyl, -NH-C₁₋₆ alkyl, -N-(C₁₋₆ alkyl)₂, -S-C₁₋₆ alkyl, -Cl, -F, -CF₃, or

25



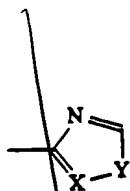
97. The compound according to claim 95, wherein -Ar₂ is:

(ii)



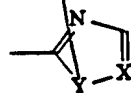
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(jj)



, or

(kk)



5

98. The compound according to claim 95,
wherein:

R_{13} is $-\text{CH}_2-\text{O}-R_9$; wherein:

10 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with $=\text{O}$ and optionally
substituted with Ar_1 .

99. The compound according to claim 95,
wherein:

R_{13} is $-\text{CH}_2-\text{S}-R_9$; wherein:

15 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with Ar_1 .

100. The compound according to claim 98,
wherein:

R_{13} is $-\text{CH}_2-\text{O}-R_9$; wherein:

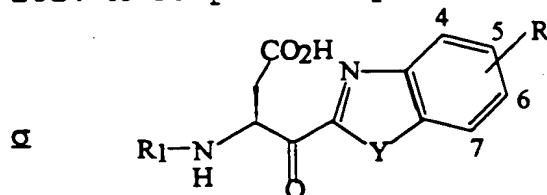
20 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with Ar_1 .

101. The compound according to claim 95,
wherein:

R_{13} is H.

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102. A compound represented by the formula:



wherein the ring is optionally substituted with one or more R groups, preferably 0, 1 or 2; and wherein:

R₁ is R₅-(A)_p-;

R₅ is selected from the group consisting of:

-H,

-Ar₁,

-CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

-SO₂-R₉,

-CO-N $\begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,

-SO₂-N $\begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,

-CO-N $\begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$, and

-SO₂-N $\begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$;

each A is independently selected from the group consisting of any α-amino acid;

p is 0, 1, 2, 3 or 4;

Y is

5 -O-,
 -S- or
 -NH; and

R is:

10 -H,
 -O-C₁₋₆ alkyl,
 -NH(C₁₋₆ alkyl),
 -N(C₁₋₆ alkyl)₂,
 -S-C₁₋₆ alkyl,
 -C₁₋₆ alkyl, or
 -Q₂;

15 each R₉ is a C₁₋₆ straight or branched alkyl group
 optionally singly or multiply substituted by -OH, -F,
 or =O and optionally substituted with one Ar₁ group;

 each R₁₀ is independently selected from the group
 consisting of -H or a C₁₋₆ straight or branched alkyl
 group;

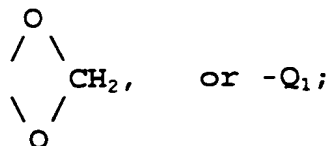
20 each T₁ is independently selected from the group
 consisting of:

25 -CH=CH-,
 -O-,
 -S-,
 -SO-,
 -SO₂-,
 -NR₁₀-,
 -NR₁₀-CO-,
 -CO-,
30 -O-CO-,

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-CO-O-,
 -CO-NR₁₀-,
 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,
 5 -NR₁₀-CO-NR₁₀-,
 -SO₂-NR₁₀-,
 -NR₁₀-SO₂-, and
 -NR₁₀-SO₂-NR₁₀-,

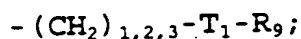
each Ar₁ is a cyclic group independently selected
 10 from the set consisting of an aryl group which
 contains 6, 10, 12, or 14 carbon atoms and between 1
 and 3 rings, a cycloalkyl group which contains
 between 3 and 15 carbon atoms and between 1 and 3
 rings, said cycloalkyl group being optionally
 15 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 =N-, and -NH-, said heterocycle group optionally
 20 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br,
 -I, -NO₂, -CN, =O, -OH,
 25 -perfluoro C₁₋₃ alkyl,



30 each Q₁ is independently selected from the group
 consisting of:

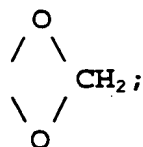
-Ar₁
 -R₉,
 -T₁-R₉, and

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each Q_2 is independently selected from the group consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $-CF_3$, and

5

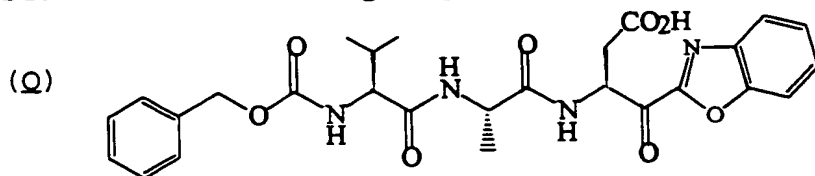


provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 .

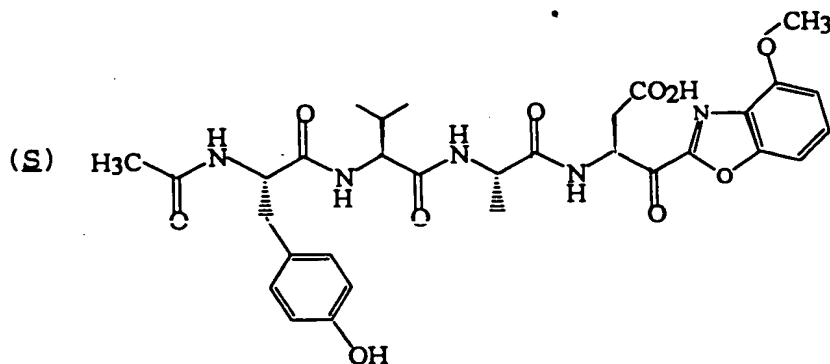
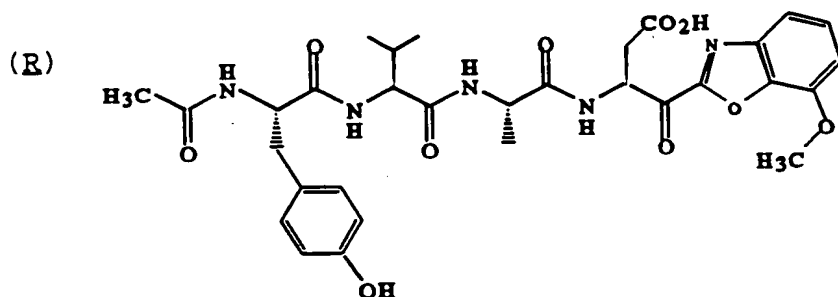
10

103. A compound according to claim 102 selected from the group consisting of:

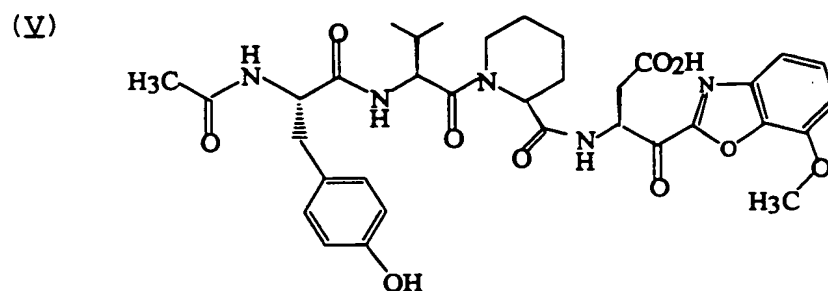
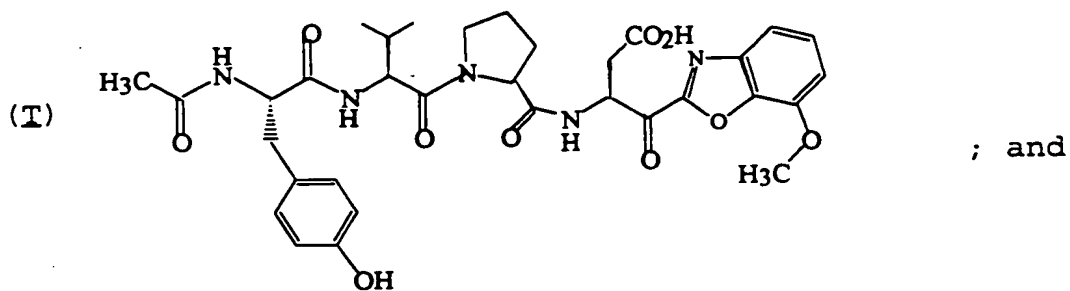
15



20



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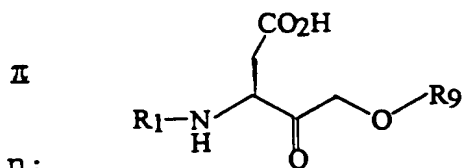


104. A compound according to claim 102 wherein each A is independently selected from the group consisting of the α -amino acids:

alanine,
 histidine,
 lysine,
 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

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105. A compound represented by the formula:



wherein:

5 R_1 is $\text{R}_5\text{--(A)}_p\text{--}$;

each T_1 is independently selected from the group consisting of:

- 10
- CH=CH-,
 - O-,
 - S-,
 - SO-,
 - SO₂-,
 - NR₁₀-,
 - NR₁₀-CO-,

15

 - CO-,
 - O-CO-,
 - CO-O-,
 - CO-NR₁₀-,
 - O-CO-NR₁₀-,

20

 - NR₁₀-CO-O-,
 - NR₁₀-CO-NR₁₀-,
 - SO₂-NR₁₀-,
 - NR₁₀-SO₂-, and
 - NR₁₀-SO₂-NR₁₀-;

25

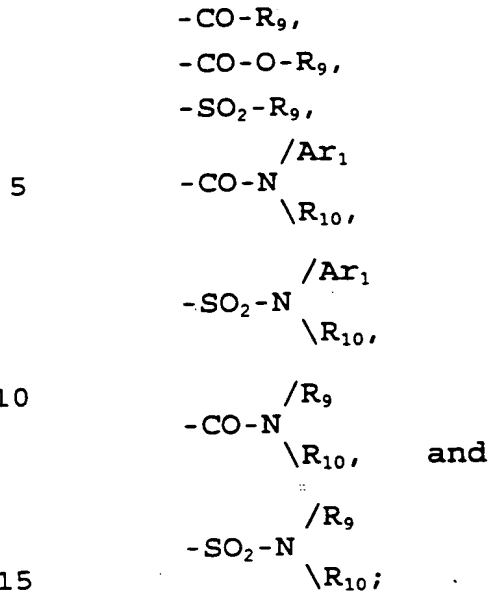
R_5 is selected from the group consisting of:

- H,
- Ar₁,
- CO-Ar₁,

30

- SO₂-Ar₁,
- R₉,

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each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

20 each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with an Ar_1 group;

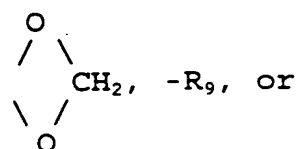
each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

25 Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said

30 cycloalkyl group being optionally benzofused, and a

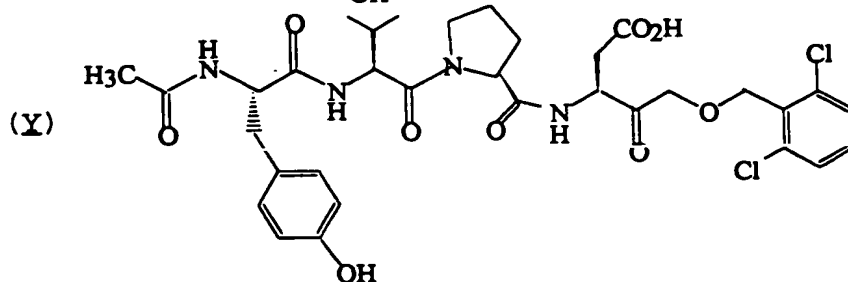
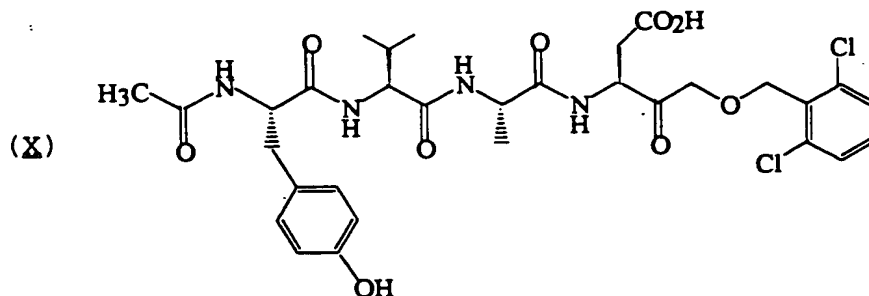
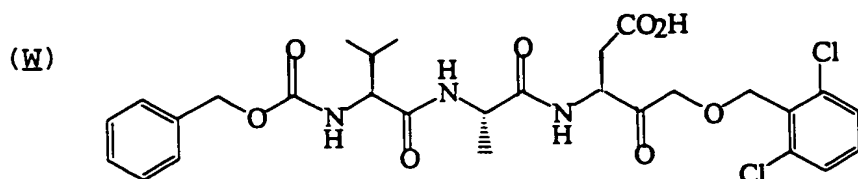
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heterocycle group containing between 5 and 15 ring
atoms and between 1 and 3 rings, said heterocycle
group containing at least one heteroatom group
selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-,
5 said heterocycle group optionally containing one or
more double bonds, said heterocycle group optionally
comprising one or more aromatic rings, and said
cyclic group optionally being singly or multiply
substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂,
10 -CH₃, =O, -OH, -perfluoro C₁₋₃ alkyl,

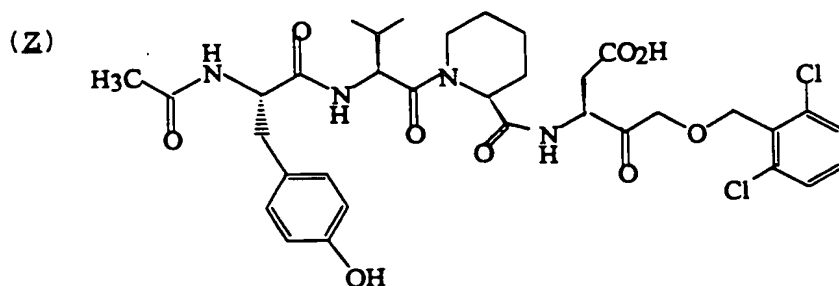


15 -T₁-R₉.

106. A compound according to claim 105
selected from the group consisting of:



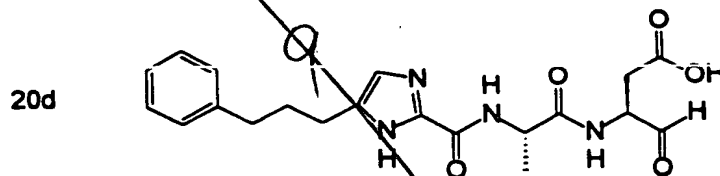
; and



107. A compound according to claim 105 wherein each A is independently selected from the group consisting of the α -amino acids:

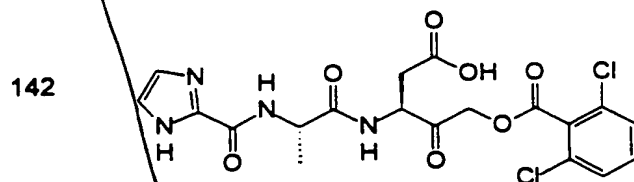
alanine,
 histidine,
 lysine,
 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

108. The compound according to claim 85, selected from the group consisting of:



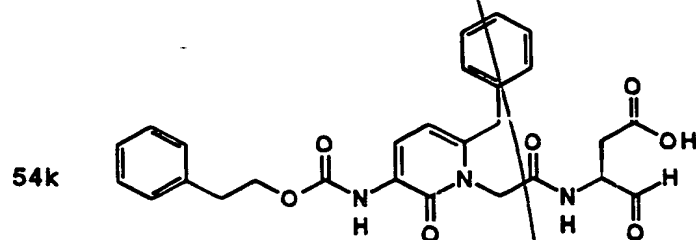
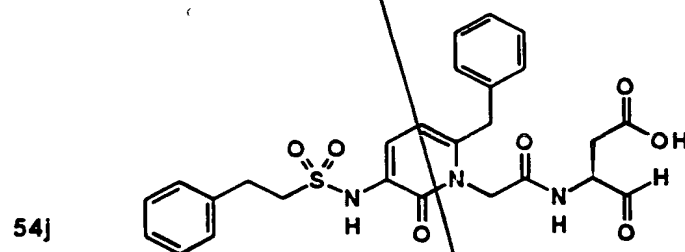
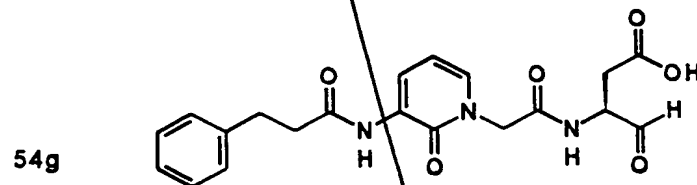
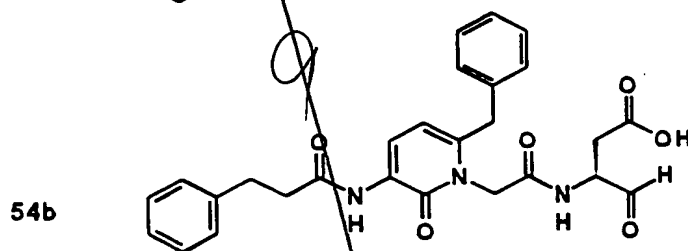
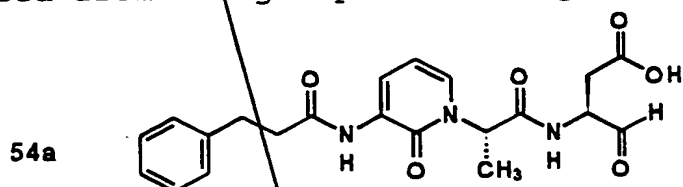
; and

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5

109. The compound according to claim 88,
selected from the group consisting of



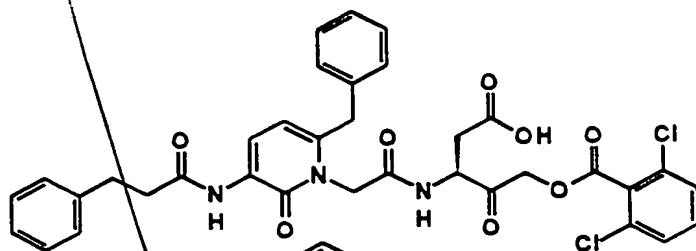
10

15

20

0988673.062401

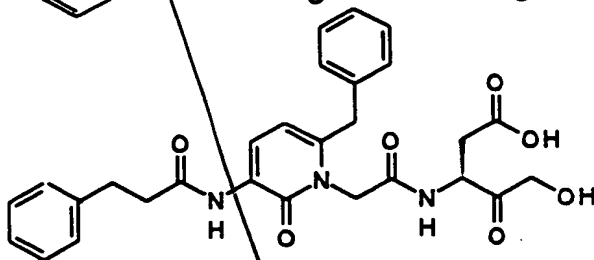
57b



;

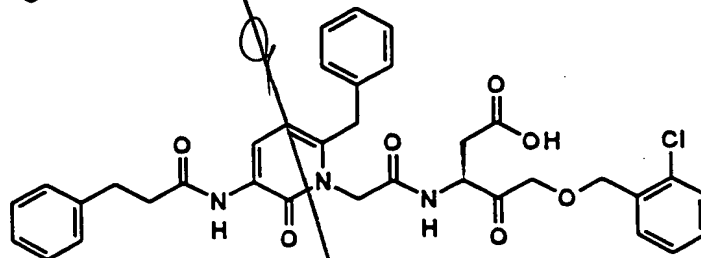
5

88



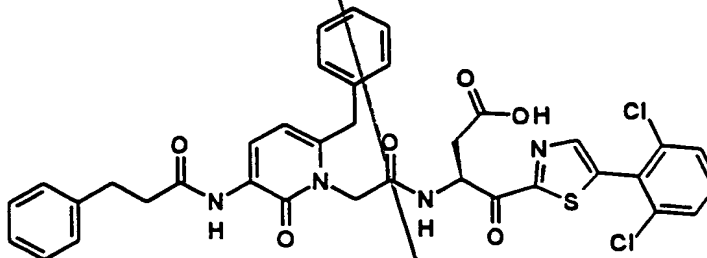
;

90



;

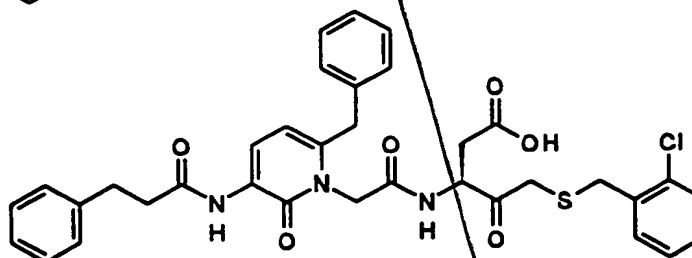
91



;

10

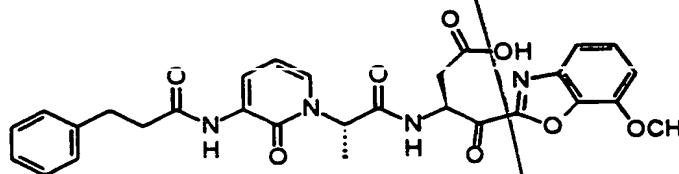
125a



;

15

126

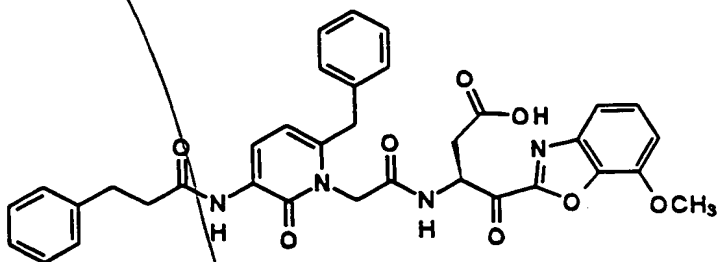


;

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5

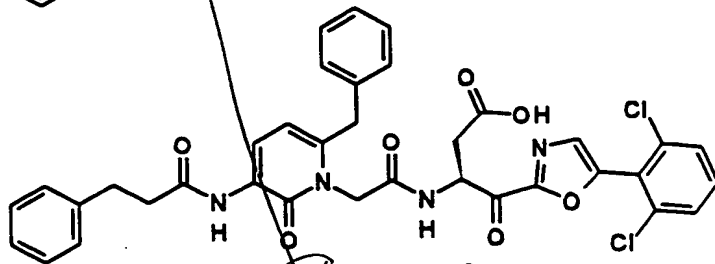
127



;

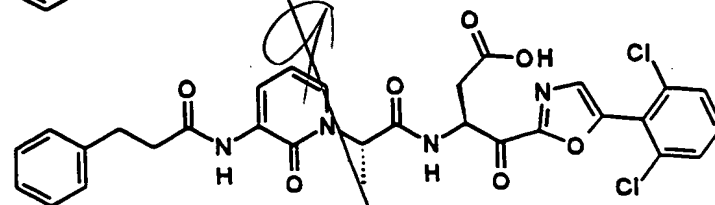
10

128



;

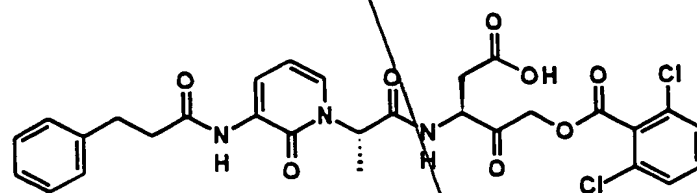
129



;

15

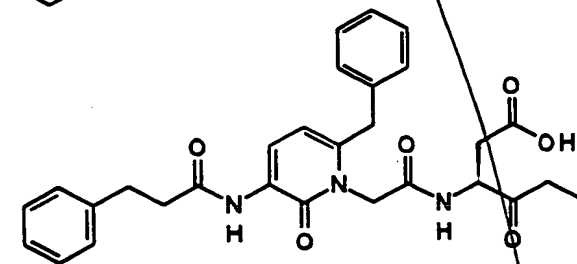
130



; and

20

131

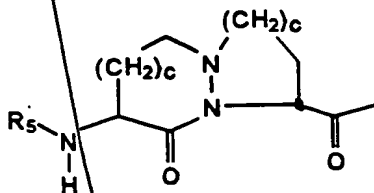


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110. The compound according to claim 89,
wherein:

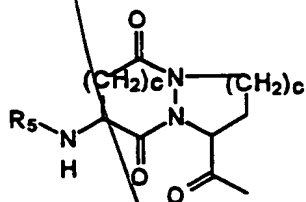
R_1 is:

(e1)



, or

(e2)



and c is 2;

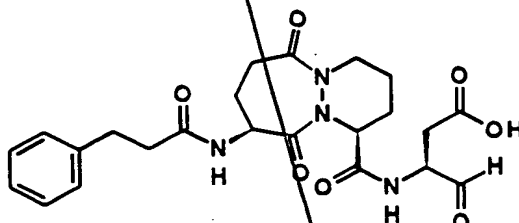
m is 1;

T is $-\text{CO}_2\text{H}$; and

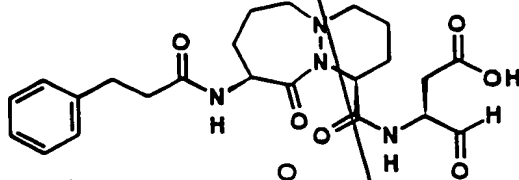
R_3 is $-\text{CO}-R_{13}$.

111. The compound according to claim 110,
selected from the group consisting of:

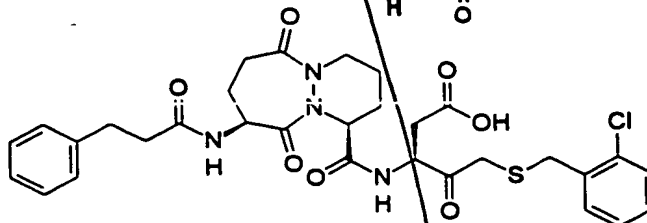
47a



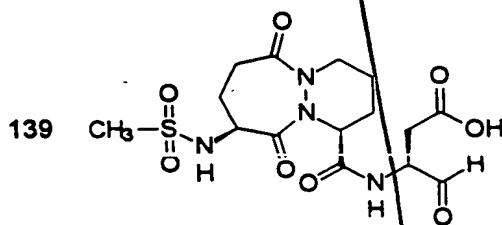
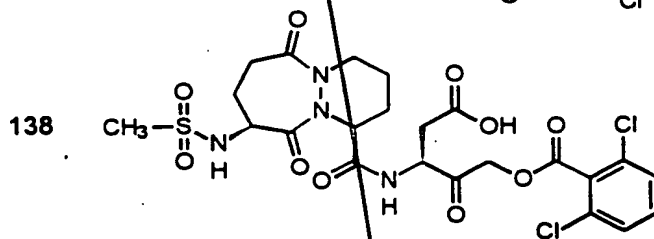
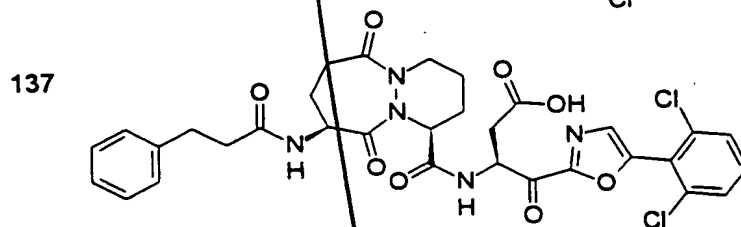
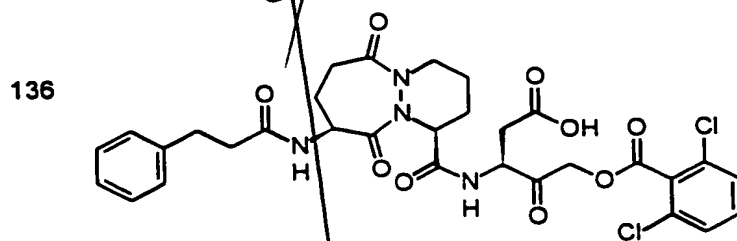
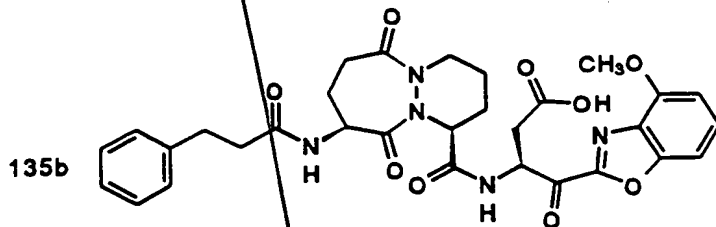
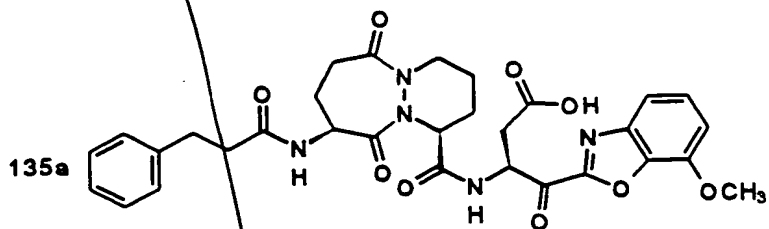
47b



125b



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;

;

;

;

; and

0988673-062101

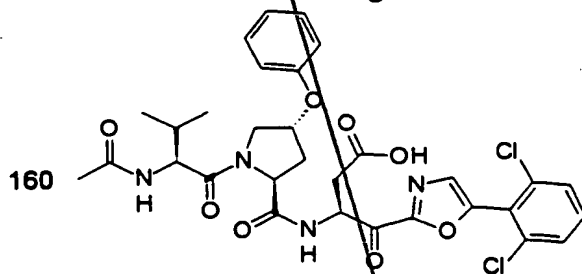
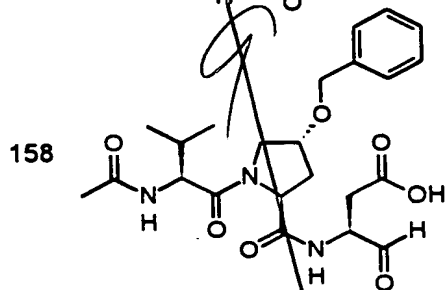
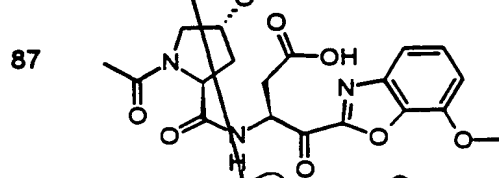
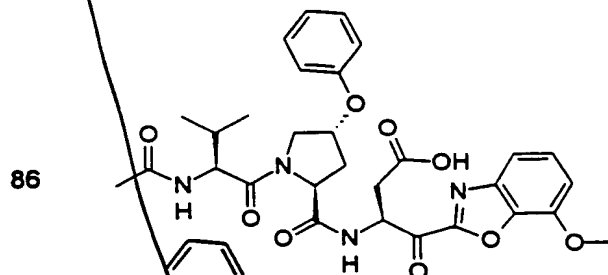
5

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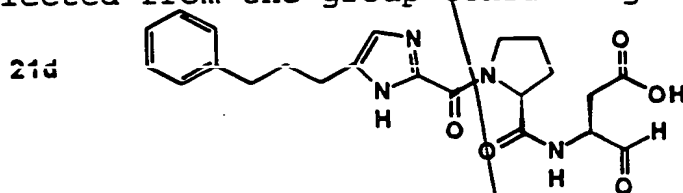
15

20

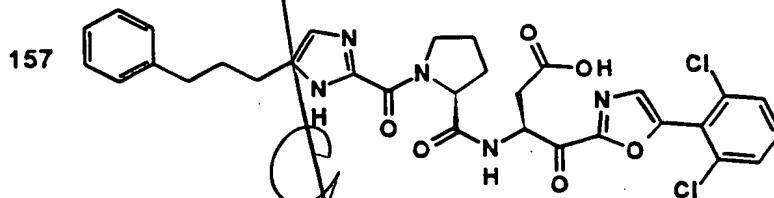
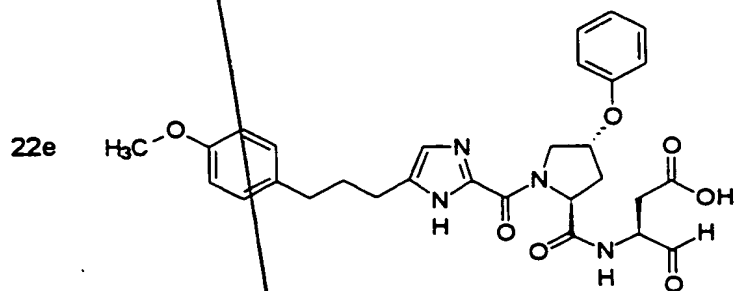
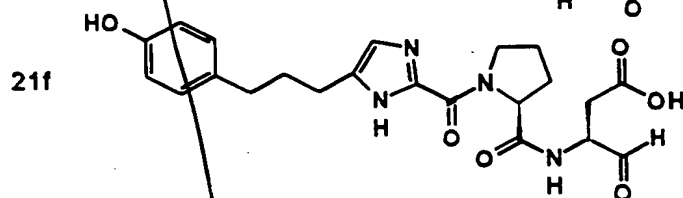
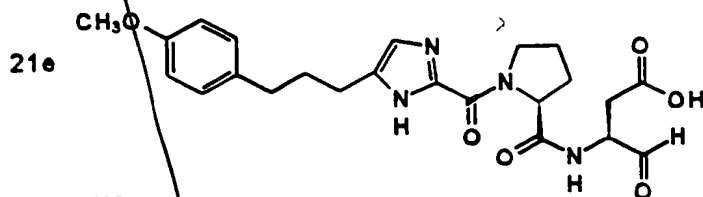
112. The compound according to claim 90,
selected from the group consisting of:



113. The compound according to claim 91,
selected from the group consisting of:



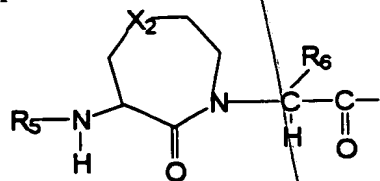
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114. The compound according to claim 84,
wherein:

R_1 is:

(o6)



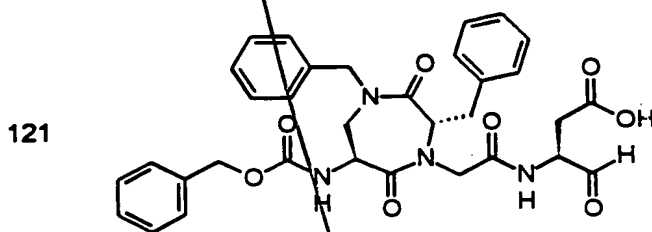
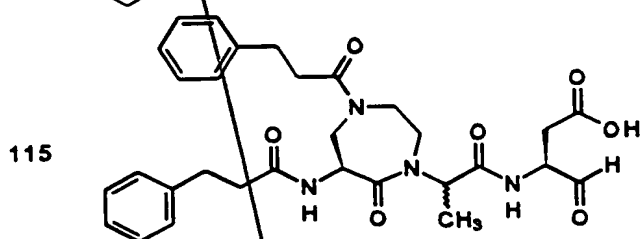
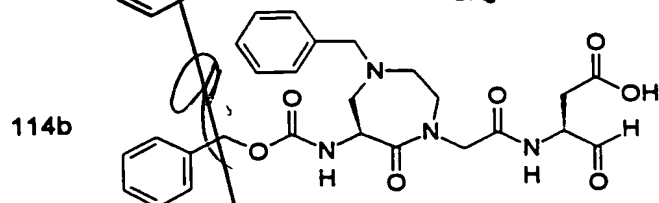
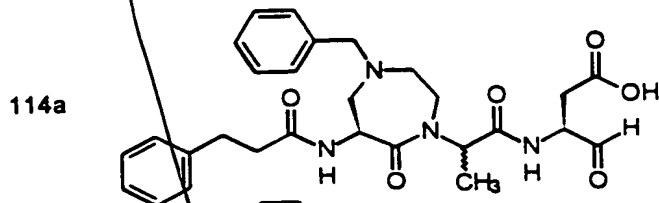
X_2 is -NH-;

m is 1;

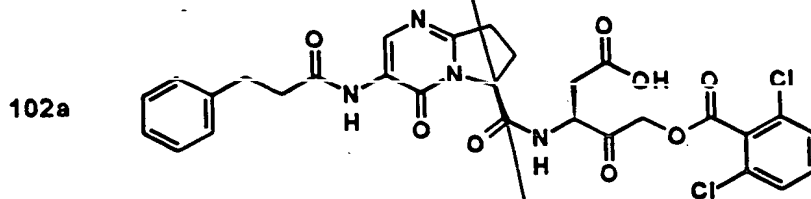
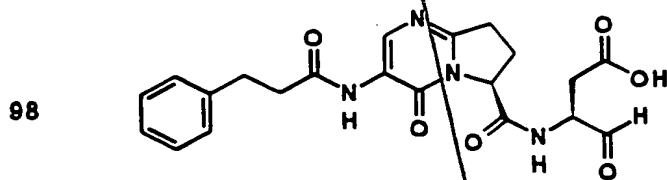
T is -CO₂H;

R_3 is -CO-R₁₃.

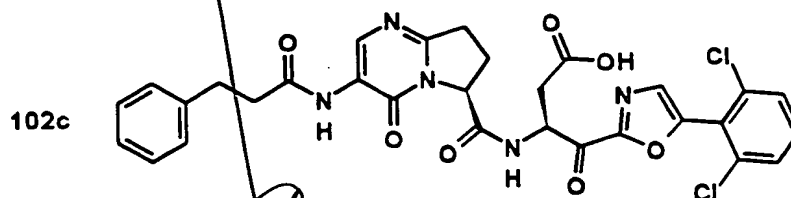
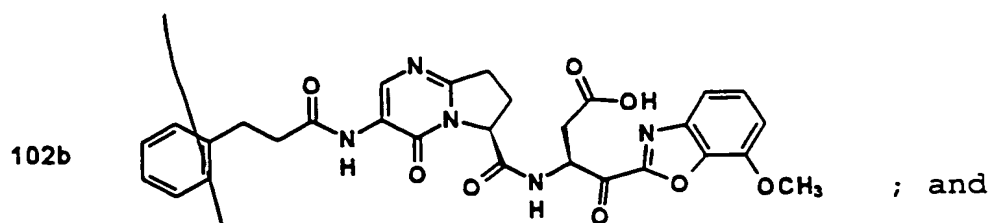
115. The compound according to claim 114,
selected from the group consisting of:



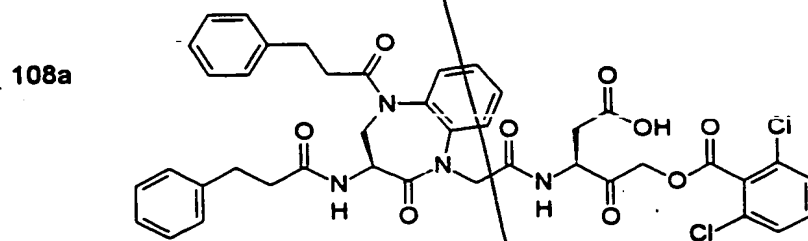
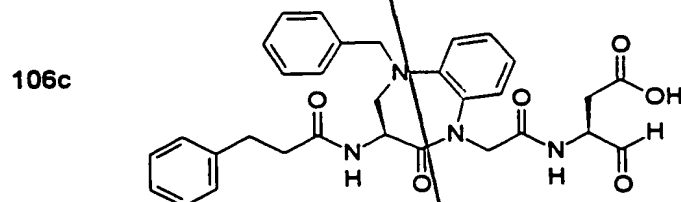
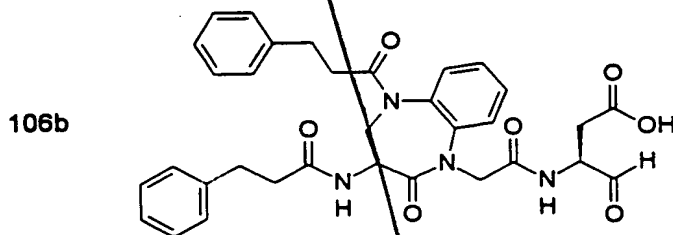
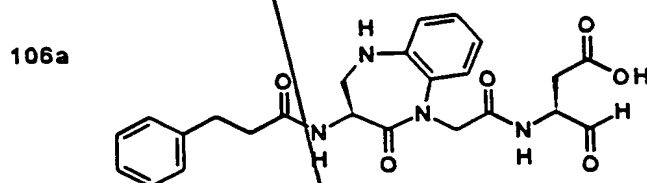
116. The compound according to claim 93,
selected from the group consisting of:



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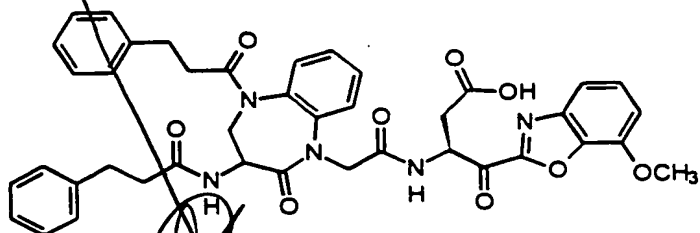


117. The compound according to claim 94,
selected from the group consisting of:



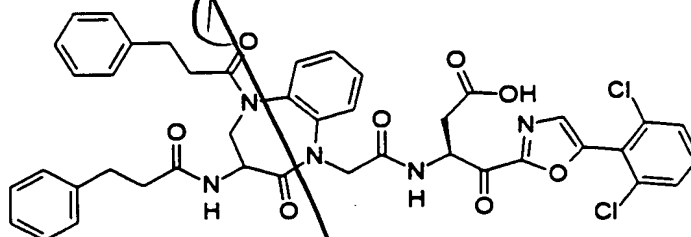
09886773-062101

108b

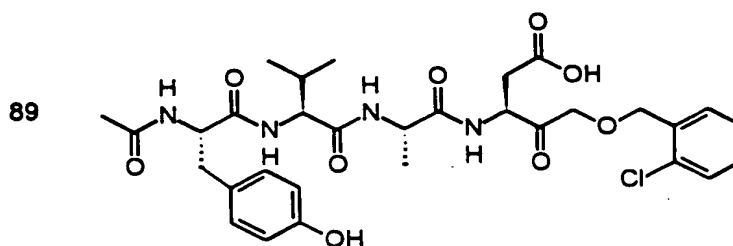


; and

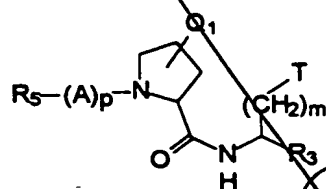
108c



118. The compound according to claim 105:



119. A compound represented by the formula:



wherein:

m is 0, 1, or 2

T is $-\text{CO}_2\text{H}$, or any bioisosteric replacement for $-\text{CO}_2\text{H}$

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R_3 is

-CN,

-CO- R_{13} , or

-CO-CO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;

R_5 is selected from the group consisting of:

-H,

-Ar₁,

-CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

-SO₂-R₉,

-CO-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,

-SO₂-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,

-CO-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$, and

-SO₂-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$;

each A is independently selected from the group consisting of any α -amino acid;

p is 2 or 3;

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F,

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or =O and optionally substituted with one Ar₁ group;

each T₁ is independently selected from the group consisting of:

- 5 -CH=CH-,
 -O-,
 -S-,
 -SO-,
 -SO₂-,
 -NR₁₀-,
10 -NR₁₀-CO-,
 -CO-,
 -O-CO-,
 -CO-O-,
 -CO-NR₁₀-,
15 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,
 -NR₁₀-CO-NR₁₀-,
 -SO₂-NR₁₀-,
 -NR₁₀-SO₂-, and
20 -NR₁₀-SO₂-NR₁₀-;

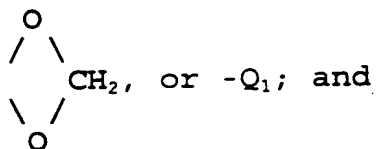
each R₁₀ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

25 each R₁₁ is independently selected from the group consisting of H, R₉, Ar₂, and -CH₂-T₁-R₉;

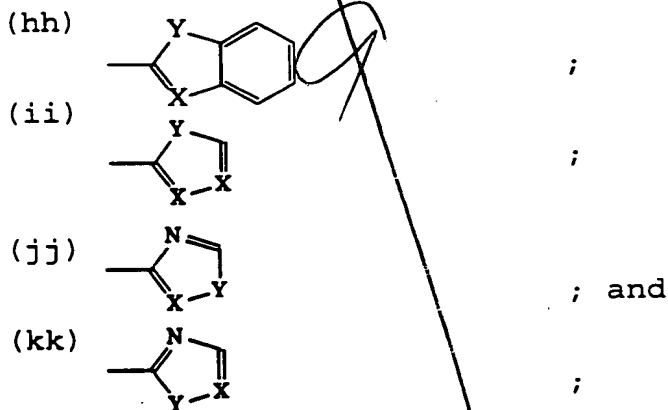
30 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

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rings, said cycloalkyl group being optionally
 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 5 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 =N-, and -NH-, said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 10 or multiply substituted by -NH₂, -CO₂H,
 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
 -perfluoro C₁₋₃ alkyl,



each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 singly or multiply substituted by -Q₁ and -Q₂:



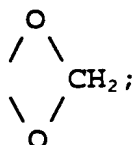
each Q₁ is independently selected from the group
 consisting of:

- Ar₁
- O-Ar₁
- R₉,

09886773-062101

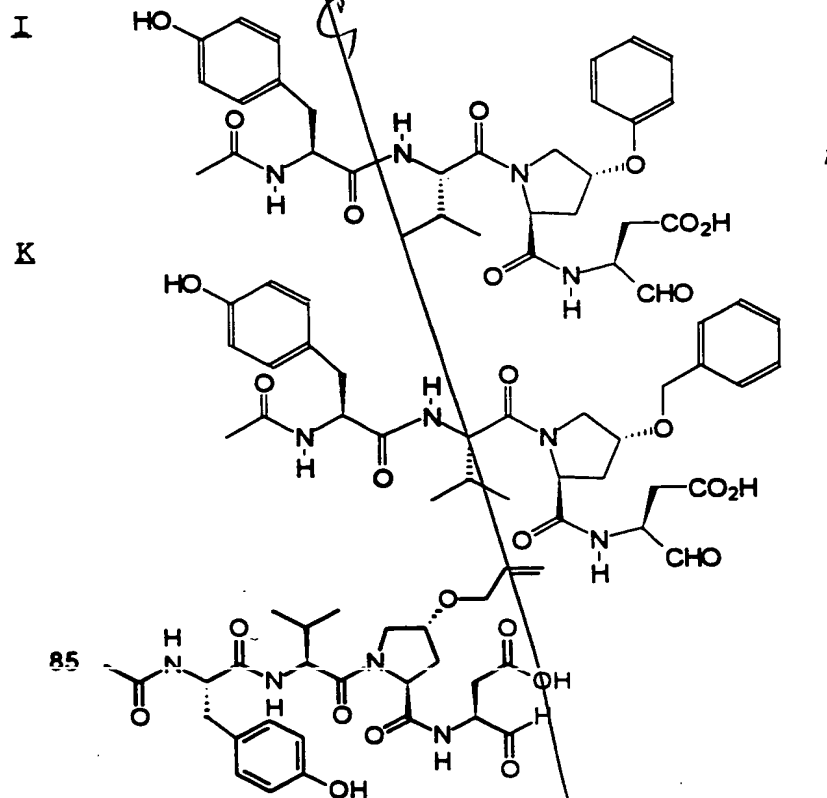
$-T_1-R_9$, and
 $-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group
 consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$,
 $-NO_2$, $-CN$, $-CF_3$, and

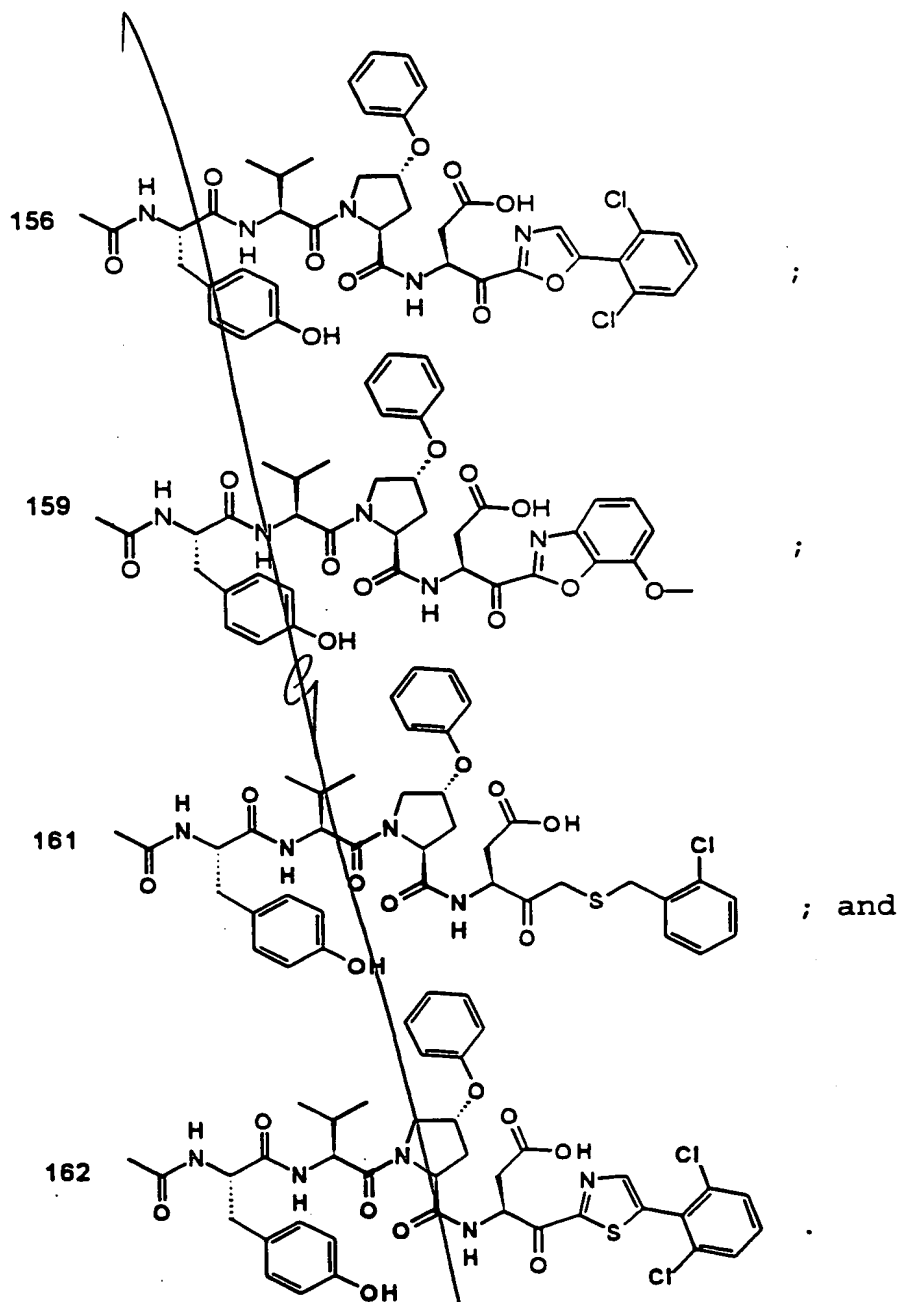


provided that when $-Ar_1$ is substituted with a Q_1
 group which comprises one or more additional $-Ar_1$
 groups, said additional $-Ar_1$ groups are not
 substituted with Q_1 .

120. The compound according to claim 119,
 selected from the group consisting of:



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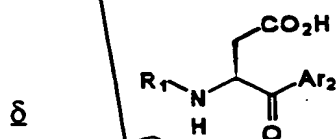


121. The compound according to claim 119,
wherein each A is independently selected from the
group consisting of the α -amino acids:

alanine,
histidine,

lysine,
phenylalanine,
proline,
tyrosine,
valine,
leucine,
isoleucine,
glutamine,
methionine,
homoproline,
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

122. A compound represented by the formula:



R_1 is $\text{R}_5-(\text{A})_p-$;

R_5 is selected from the group consisting of:

- H,
- Ar_1 ,
- CO- Ar_1 ,
- SO₂- Ar_1 ,
- R_9 ,
- CO- R_9 ,
- CO-O- R_9 ,
- SO₂- R_9 ,
- CO-N $\begin{array}{l} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{array}$,

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$$\begin{array}{l} \text{---SO}_2\text{---N} \begin{array}{l} \nearrow \text{Ar}_1 \\ \searrow \text{R}_{10}, \end{array} \end{array}$$
$$-\text{CO}-\text{N} \begin{array}{l} \nearrow \text{R}_9 \\ \searrow \text{R}_{10}, \end{array} \quad \text{and}$$
$$-\text{SO}_2-\text{N} \begin{array}{l} \diagup \text{R}_9 \\ \diagdown \text{R}_{10}; \end{array}$$

10 each A_i is independently selected from the group
consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each T_1 is independently selected from the group
20 consisting of:

$$-\text{CH}=\text{CH}-,$$

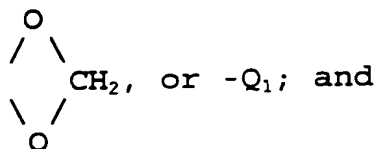
-O-

-S-

-SO-

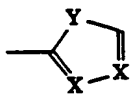
25 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

rings, said cycloalkyl group being optionally
benzofused, and a heterocycle group containing
between 5 and 15 ring atoms and between 1 and 3
rings, said heterocycle group containing at least one
heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
=N-, and -NH-, said heterocycle group optionally
containing one or more double bonds, said heterocycle
group optionally comprising one or more aromatic
rings, and said cyclic group optionally being singly
or multiply substituted by -NH₂, -CO₂H,
-Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
-perfluoro C₁₋₃ alkyl,



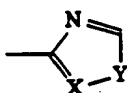
each Ar₂ is independently selected from the
following group, in which any ring may optionally be
singly or multiply substituted by -Q₁ and -Q₂:

(ii)



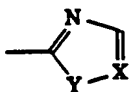
;

(jj)



; and

(kk)



;

each Q₁ is independently selected from the group
consisting of:

-Ar₁

-O-Ar₁

-R₉,

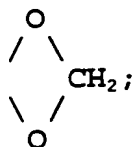
-T₁-R₉,

and

$-(CH_2)_{1,2,3}-T_1-R_9;$

each Q_2 is independently selected from the group consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$,

$-NO_2$, $-CN$, $-CF_3$, and

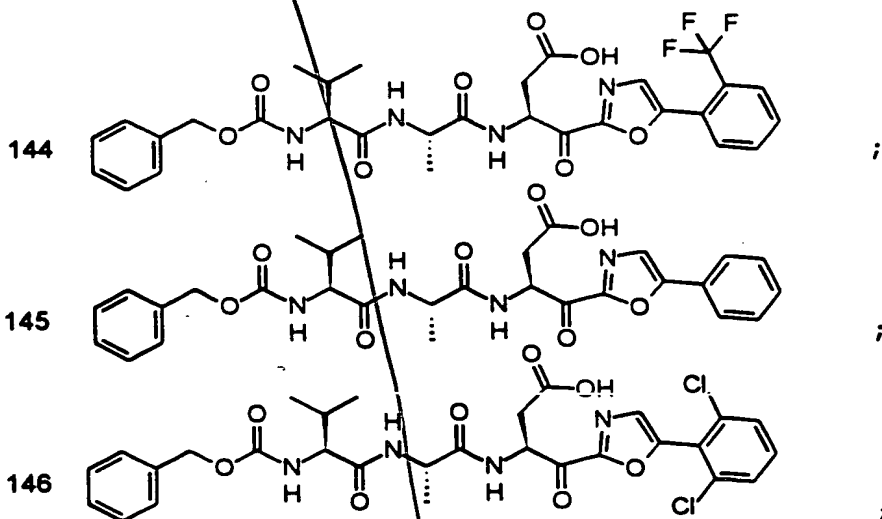


provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

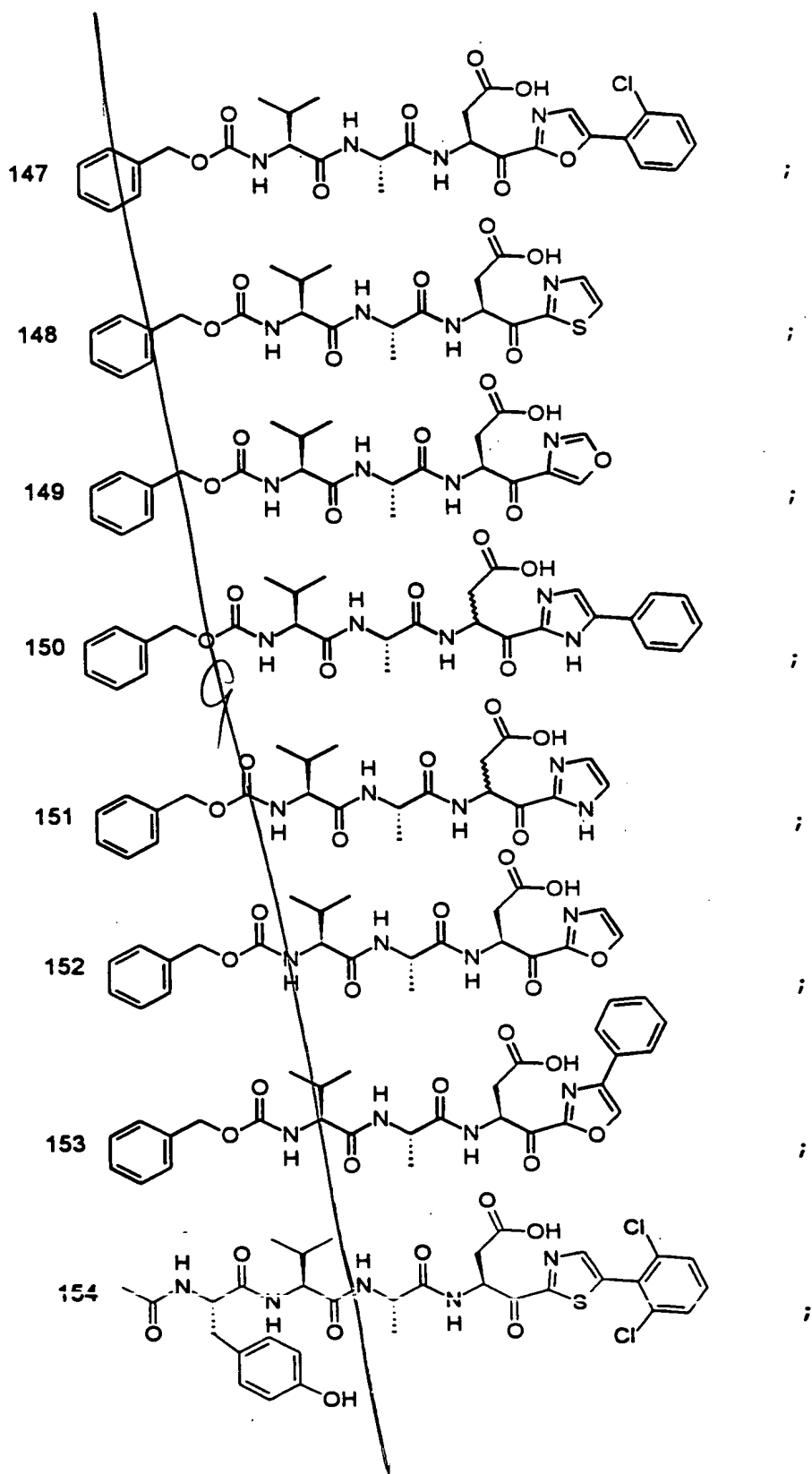
each X is independently selected from the group consisting of $=N-$, and $=CH-$; and

each Y is independently selected from the group consisting of $-O-$, $-S-$, and $-NH$.

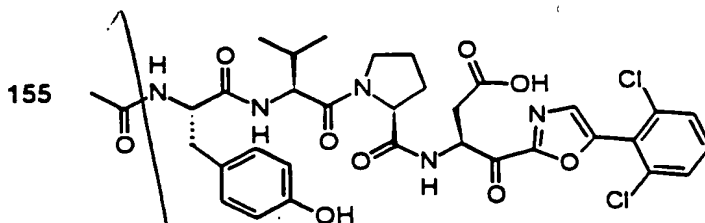
123. The compound according to claim 122, selected from the group consisting of:



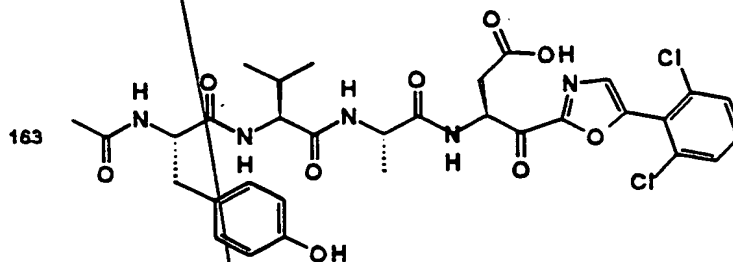
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; and



124. The compound according to claim 122,
wherein each A is independently selected from the
group consisting of the α -amino acids:

alanine,
histidine,
lysine,
phenylalanine,
proline,
tyrosine,
valine,
leucine,
isoleucine,
glutamine,
methionine,
homoproline,
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

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Add
a2